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- (71) Applicant (for all designated States except US): **AMGEN, INC.** [US/US]; One Amgen Center Drive, Mailstop 27-4-A, Thousand Oaks, CA 91320-1789 (US).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **PASZTY, Christopher, J.** [US/US]; 1027 Westridge Drive, Ventura, CA 93003 (US). **GONG, Jianhua** [CN/US]; 2489 Gillingham Circle, Thousand Oaks, CA 91362 (US). **DAUGHERTY, Betsy** [US/US]; 3091 Stonewood Street, Simi Valley, CA 93062 (US). **ROGERS, Norma** [US/US]; 4042 Milano Place, Moorpark, CA 93021 (US).
- (74) Agent: **ZUHN, Donald, L.**; McDonnell Boehnen Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).
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(54) Title: **LEUCINE-RICH REPEAT-CONTAINING G-PROTEIN COUPLED RECEPTOR-8 MOLECULES AND USES THEREOF**

(57) Abstract: The present invention provides Leucine-Rich Repeat-Containing G-Protein Coupled Receptor-8 (LGR8) polypeptides and nucleic acid molecules encoding the same. The invention also provides selective binding agents, vectors, host cells, and methods for producing LGR8 polypeptides. The invention further provides pharmaceutical compositions and methods for the diagnosis, treatment, amelioration, and/or prevention of diseases, disorders, and conditions associated with LGR8 polypeptides.



WO 02/14489 A2

LEUCINE-RICH REPEAT-CONTAINING G-PROTEIN COUPLED RECEPTOR-8 MOLECULES AND USES THEREOF

This application claims the benefit of priority from U.S. Provisional Patent
5 Application No. 60/224,455, filed on August 10, 2000, the disclosure of which is
explicitly incorporated by reference herein.

Field of the Invention

The present invention relates to Leucine-Rich Repeat-Containing G-Protein
10 Coupled Receptor-8 (LGR8) polypeptides and nucleic acid molecules encoding the
same. The invention also relates to selective binding agents, vectors, host cells, and
methods for producing LGR8 polypeptides. The invention further relates to
pharmaceutical compositions and methods for the diagnosis, treatment, amelioration,
and/or prevention of diseases, disorders, and conditions associated with LGR8
15 polypeptides.

Background of the Invention

Technical advances in the identification, cloning, expression, and
manipulation of nucleic acid molecules and the deciphering of the human genome
20 have greatly accelerated the discovery of novel therapeutics. Rapid nucleic acid
sequencing techniques can now generate sequence information at unprecedented rates
and, coupled with computational analyses, allow the assembly of overlapping
sequences into partial and entire genomes and the identification of polypeptide-
encoding regions. A comparison of a predicted amino acid sequence against a
25 database compilation of known amino acid sequences allows one to determine the
extent of homology to previously identified sequences and/or structural landmarks.
The cloning and expression of a polypeptide-encoding region of a nucleic acid
molecule provides a polypeptide product for structural and functional analyses. The
manipulation of nucleic acid molecules and encoded polypeptides may confer
30 advantageous properties on a product for use as a therapeutic.

In spite of the significant technical advances in genome research over the past
decade, the potential for the development of novel therapeutics based on the human
genome is still largely unrealized. Many genes encoding potentially beneficial
polypeptide therapeutics or those encoding polypeptides, which may act as "targets"

The present invention further relates to four distinct LGR8 alternative splicing variants. The LGR8-A coding sequence consists of 18 coding exons that encode a large N-terminal leucine-rich repeat-containing extracellular domain, seven predicted transmembrane domains, and a cytoplasmic C-terminal region. The LGR8-B coding sequence is identical to the LGR8-A coding sequence with the exception that the LGR8-B coding sequence lacks one of the exons encoding the N-terminal extracellular domain. The LGR8-C coding sequence is identical to the LGR8-A coding sequence with the exception that the LGR8-C coding sequence lacks three of the exons encoding the N-terminal extracellular domain. The LGR8-D coding sequence consists of exons encoding approximately 90% of the N-terminal extracellular domain of the LGR8-B coding sequence, but lacks exons encoding the transmembrane domains and the cytoplasmic C-terminal region. Thus, LGR8-D is a secreted, N-terminal extracellular domain version of LGR8-B and likely functions as an antagonist of the LGR8 signaling pathway. LGR8-D is truncated very near the C-terminal end of the N-terminal extracellular domain by virtue of the fact that an additional exon, which contains stop codons, is spliced in just 5' of the exon which encodes the first transmembrane domain of LGR8-A, LGR8-B, and LGR8-C. It is likely that the N-terminal extracellular domains of LGR8-A, LGR8-B, and LGR8-C would be able to function as antagonists of the LGR8 signaling pathway.

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The invention provides for an isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

(a) the nucleotide sequence as set forth in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22;

(b) a nucleotide sequence encoding the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(c) a nucleotide sequence which hybridizes under moderately or highly stringent conditions to the complement of either (a) or (b); and

(d) a nucleotide sequence complementary to either (a) or (b).

30

(a) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

10 (b) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one amino acid insertion, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

20 (c) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one amino acid deletion, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

30 (d) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 which has a C- and/or N- terminal truncation, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ

(c) an amino acid sequence which is at least about 70 percent identical to the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(d) a fragment of the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 comprising at least about 25 amino acid residues, wherein the fragment has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or is antigenic; and

(e) an amino acid sequence for an allelic variant or splice variant of the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or any of (a) - (c).

The invention further provides for an isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

(a) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

The invention still further provides for an isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution selected from the group consisting of: isoleucine at position 26; valine at position 41; isoleucine at position 55; aspartic acid at position 78; aspartic acid at position 123; arginine at position 130; valine at position 135; methionine at position 142; leucine at position 166; tyrosine at position 167; lysine at position 201; valine at position 204; isoleucine at position 216; glutamatic acid at position 217; leucine at position 221; leucine at position 240; leucine at position 252; isoleucine at position 277; methionine at position 288; lysine at position 290; isoleucine at position 324; isoleucine at position 341; isoleucine at position 344; aspartic acid at position 350; leucine at position 376; valine at position 420; valine at position 425; valine at position 427; isoleucine at position 434; tyrosine at position 442; arginine at position 444; tyrosine at position 450; isoleucine at position 466; isoleucine at position 471; leucine at position 476; phenylalanine at position 478; glutamatic acid at position 481; histidine at position 485; phenylalanine at position 515; tyrosine at position 521; isoleucine at position 522; tyrosine at position 526; valine at position 531; valine at position 541; isoleucine at position 551; valine at position 552; glutamatic acid at position 561; phenylalanine at position 562; tyrosine at position 566; tyrosine at position 577; aspartic acid at position 579; isoleucine at position 597; isoleucine at position 603; valine at position 616; isoleucine at position 621; isoleucine at position 626; lysine at position 632; leucine at position 649; isoleucine at position 654; valine at position 675; isoleucine at position 682; glutamatic acid at position 700; isoleucine at position 702; tyrosine at position 707; tyrosine at position 709; isoleucine at position 727; valine at position 729; methionine at position 737; methionine at position 745; and leucine at position 749; wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2.

Also provided are fusion polypeptides comprising LGR8 amino acid sequences.

The present invention also provides for an expression vector comprising the isolated nucleic acid molecules as set forth herein, recombinant host cells comprising the recombinant nucleic acid molecules as set forth herein, and a method of producing

Methods of regulating expression and modulating (*i.e.*, increasing or decreasing) levels of an LGR8 polypeptide are also encompassed by the invention. One method comprises administering to an animal a nucleic acid molecule encoding an LGR8 polypeptide. In another method, a nucleic acid molecule comprising
5 elements that regulate or modulate the expression of an LGR8 polypeptide may be administered. Examples of these methods include gene therapy, cell therapy, and anti-sense therapy as further described herein.

LGR8 polypeptides can be used for identifying ligands thereof. Various forms of "expression cloning" have been used for cloning ligands for receptors (*See, e.g.*,
10 Davis *et al.*, 1996, *Cell*, 87:1161-69). These and other LGR8 ligand cloning experiments are described in greater detail herein. Isolation of the LGR8 ligand(s) allows for the identification or development of novel agonists and/or antagonists of the LGR8 signaling pathway. Such agonists and antagonists include LGR8 ligand(s), anti-LGR8 ligand antibodies and derivatives thereof, small molecules, or antisense
15 oligonucleotides, any of which can be used for potentially treating one or more diseases or disorders, including those recited herein.

Brief Description of the Figures

Figures 1A-1D illustrate a nucleotide sequence (SEQ ID NO: 1) encoding human
20 LGR8-A (SEQ ID NO: 2). The predicted signal sequence is indicated (underline);

Figures 2A-2B illustrate a nucleotide sequence (SEQ ID NO: 4) encoding the N-terminal extracellular domain (absent the signal peptide) of human LGR8-A (SEQ ID
25 NO: 5);

Figures 3A-3D illustrate a nucleotide sequence (SEQ ID NO: 6) encoding human LGR8-B (SEQ ID NO: 7). The predicted signal sequence is indicated (underline);

Figures 4A-4B illustrate a nucleotide sequence (SEQ ID NO: 9) encoding the N-terminal extracellular domain (absent the signal peptide) of human LGR8-B (SEQ ID
30 NO: 10);

Figures 5A-5D illustrate a nucleotide sequence (SEQ ID NO: 11) encoding human LGR8-C (SEQ ID NO: 12). The predicted signal sequence is indicated (underline);

transmembrane domains, and a C-terminal cytoplasmic domain. Accordingly, LGR8-A, LGR8-B, and LGR8-C are useful as targets for agonistic or antagonistic molecules, including, but not limited to, antibodies, fusion polypeptides, carbohydrates, polynucleotides (such as antisense oligonucleotides), or small molecular weight
5 organic molecules.

Additionally, it will be understood that the N-terminal extracellular domains of LGR8-A, LGR8-B, and LGR8-C can be used as antagonists of the LGR8 signaling pathway, for example, where the N-terminal extracellular domain is fused to an Fc portion of an antibody.

10 It will also be appreciated that LGR8-D is a secreted form of the N-terminal extracellular domain of LGR8-B. In this regard LGR8-D may act as an antagonist of the LGR8-B ligand(s). LGR8-D can be used as a target for antagonistic and agonistic molecules, including, but not limited to, antibodies, fusion polypeptides, carbohydrates, polynucleotides (such as antisense oligonucleotides), or small
15 molecular weight organic molecules. For example, an antagonist specific for LGR8-D would inhibit the antagonistic activity of LGR8-D, thus enhancing the activity of LGR8-D ligand(s) and/or enhancing signaling through LGR8 receptors. Conversely an agonist specific for LGR8-D would enhance the antagonistic activity of LGR8-D, thus diminishing the activity of LGR8-D ligand(s) and/or diminishing signaling
20 through LGR8.

Definitions

The terms "LGR8 gene" or "LGR8 nucleic acid molecule" or "LGR8 polynucleotide" refer to a nucleic acid molecule comprising or consisting of a
25 nucleotide sequence as set forth in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22, a nucleotide sequence encoding the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ
30 ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, and nucleic acid molecules as defined herein.

The term "LGR8 polypeptide allelic variant" refers to one of several possible naturally occurring alternate forms of a gene occupying a given locus on a chromosome of an organism or a population of organisms.

The term "vector" is used to refer to any molecule (*e.g.*, nucleic acid, plasmid, or virus) used to transfer coding information to a host cell.

The term "expression vector" refers to a vector that is suitable for transformation of a host cell and contains nucleic acid sequences that direct and/or control the expression of inserted heterologous nucleic acid sequences. Expression includes, but is not limited to, processes such as transcription, translation, and RNA splicing, if introns are present.

The term "operably linked" is used herein to refer to an arrangement of flanking sequences wherein the flanking sequences so described are configured or assembled so as to perform their usual function. Thus, a flanking sequence operably linked to a coding sequence may be capable of effecting the replication, transcription and/or translation of the coding sequence. For example, a coding sequence is operably linked to a promoter when the promoter is capable of directing transcription of that coding sequence. A flanking sequence need not be contiguous with the coding sequence, so long as it functions correctly. Thus, for example, intervening untranslated yet transcribed sequences can be present between a promoter sequence and the coding sequence and the promoter sequence can still be considered "operably linked" to the coding sequence.

The term "host cell" is used to refer to a cell which has been transformed, or is capable of being transformed with a nucleic acid sequence and then of expressing a selected gene of interest. The term includes the progeny of the parent cell, whether or not the progeny is identical in morphology or in genetic make-up to the original parent, so long as the selected gene is present.

The term "LGR8 polypeptide" refers to a polypeptide comprising the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 and related polypeptides. Related polypeptides include LGR8 polypeptide fragments, LGR8 polypeptide orthologs, LGR8 polypeptide variants, and LGR8 polypeptide derivatives, which possess at least one activity of the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. LGR8 polypeptides may be mature polypeptides, as defined herein, and may or may

polypeptides) as compared to the LGR8 polypeptide amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 (with or
5 without a leader sequence). Variants may be naturally occurring (*e.g.*, LGR8 polypeptide allelic variants, LGR8 polypeptide orthologs, and LGR8 polypeptide splice variants) or artificially constructed. Such LGR8 polypeptide variants may be prepared from the corresponding nucleic acid molecules having a DNA sequence that varies accordingly from the DNA sequence as set forth in any of SEQ ID NO: 1, SEQ
10 ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22. In preferred embodiments, the variants have from 1 to 3, or from 1 to 5, or from 1 to 10, or from 1 to 15, or from 1 to 20, or from 1 to 25, or from 1 to 50, or from 1 to 75, or from 1 to 100, or more than 100 amino acid substitutions, insertions, additions and/or deletions, wherein the
15 substitutions may be conservative, or non-conservative, or any combination thereof.

The term "LGR8 polypeptide derivatives" refers to the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23,
20 LGR8 polypeptide fragments, LGR8 polypeptide orthologs, or LGR8 polypeptide variants, as defined herein, that have been chemically modified. The term "LGR8 polypeptide derivatives" also refers to the polypeptides encoded by LGR8 polypeptide allelic variants or LGR8 polypeptide splice variants, as defined herein, that have been chemically modified.

25 The term "mature LGR8 polypeptide" refers to an LGR8 polypeptide lacking a leader sequence. A mature LGR8 polypeptide may also include other modifications such as proteolytic processing of the amino-terminus (with or without a leader sequence) and/or the carboxyl-terminus, cleavage of a smaller polypeptide from a larger precursor, N-linked and/or O-linked glycosylation, and the like. Exemplary
30 mature CHL2 polypeptides are depicted by the amino acid sequences of SEQ ID NO: 3, SEQ ID NO: 8, SEQ ID NO: 13, SEQ ID NO: 18, OR SEQ ID NO: 21.

The term "LGR8 fusion polypeptide" refers to a fusion of one or more amino acids (such as a heterologous protein or peptide) at the amino- or carboxyl-terminus of the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO:

alignments (if any) addressed by a particular mathematical model or computer program (*i.e.*, "algorithms").

The term "similarity" is a related concept, but in contrast to "identity," "similarity" refers to a measure of relatedness that includes both identical matches and conservative substitution matches. If two polypeptide sequences have, for example, 10/20 identical amino acids, and the remainder are all non-conservative substitutions, then the percent identity and similarity would both be 50%. If in the same example, there are five more positions where there are conservative substitutions, then the percent identity remains 50%, but the percent similarity would be 75% (15/20). Therefore, in cases where there are conservative substitutions, the percent similarity between two polypeptides will be higher than the percent identity between those two polypeptides.

The term "naturally occurring" or "native" when used in connection with biological materials such as nucleic acid molecules, polypeptides, host cells, and the like, refers to materials which are found in nature and are not manipulated by man. Similarly, "non-naturally occurring" or "non-native" as used herein refers to a material that is not found in nature or that has been structurally modified or synthesized by man.

The terms "effective amount" and "therapeutically effective amount" each refer to the amount of an LGR8 polypeptide or LGR8 nucleic acid molecule used to support an observable level of one or more biological activities of the LGR8 polypeptides as set forth herein.

The term "pharmaceutically acceptable carrier" or "physiologically acceptable carrier" as used herein refers to one or more formulation materials suitable for accomplishing or enhancing the delivery of the LGR8 polypeptide, LGR8 nucleic acid molecule, or LGR8 selective binding agent as a pharmaceutical composition.

The term "antigen" refers to a molecule or a portion of a molecule capable of being bound by a selective binding agent, such as an antibody, and additionally capable of being used in an animal to produce antibodies capable of binding to an epitope of that antigen. An antigen may have one or more epitopes.

The term "selective binding agent" refers to a molecule or molecules having specificity for an LGR8 polypeptide. As used herein, the terms, "specific" and "specificity" refer to the ability of the selective binding agents to bind to human LGR8 polypeptides and not to bind to human non-LGR8 polypeptides. It will be

residues compared to the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. Such related LGR8 polypeptides may
5 comprise, for example, an addition and/or a deletion of one or more N-linked or O-linked glycosylation sites or an addition and/or a deletion of one or more cysteine residues.

Related nucleic acid molecules also include fragments of LGR8 nucleic acid molecules which encode a polypeptide of at least about 25 contiguous amino acids, or
10 about 50 amino acids, or about 75 amino acids, or about 100 amino acids, or about 150 amino acids, or about 200 amino acids, or more than 200 amino acid residues of the LGR8 polypeptide of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or
15 SEQ ID NO: 23.

In addition, related LGR8 nucleic acid molecules also include those molecules which comprise nucleotide sequences which hybridize under moderately or highly stringent conditions as defined herein with the fully complementary sequence of the LGR8 nucleic acid molecule of any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6,
20 SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22, or of a molecule encoding a polypeptide, which polypeptide comprises the amino acid sequence as shown in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20,
25 SEQ ID NO: 21, or SEQ ID NO: 23, or of a nucleic acid fragment as defined herein, or of a nucleic acid fragment encoding a polypeptide as defined herein. Hybridization probes may be prepared using the LGR8 sequences provided herein to screen cDNA, genomic or synthetic DNA libraries for related sequences. Regions of the DNA and/or amino acid sequence of LGR8 polypeptide that exhibit significant identity to
30 known sequences are readily determined using sequence alignment algorithms as described herein and those regions may be used to design probes for screening.

The term "highly stringent conditions" refers to those conditions that are designed to permit hybridization of DNA strands whose sequences are highly complementary, and to exclude hybridization of significantly mismatched DNAs.

stringent conditions" are 0.015 M sodium chloride, 0.0015 M sodium citrate at 50-65°C or 0.015 M sodium chloride, 0.0015 M sodium citrate, and 20% formamide at 37-50°C. By way of example, "moderately stringent conditions" of 50°C in 0.015 M sodium ion will allow about a 21% mismatch.

5 It will be appreciated by those skilled in the art that there is no absolute distinction between "highly stringent conditions" and "moderately stringent conditions." For example, at 0.015 M sodium ion (no formamide), the melting temperature of perfectly matched long DNA is about 71°C. With a wash at 65°C (at the same ionic strength), this would allow for approximately a 6% mismatch. To
10 capture more distantly related sequences, one skilled in the art can simply lower the temperature or raise the ionic strength.

A good estimate of the melting temperature in 1M NaCl* for oligonucleotide probes up to about 20nt is given by:

$$T_m = 2^{\circ}\text{C per A-T base pair} + 4^{\circ}\text{C per G-C base pair}$$

15 *The sodium ion concentration in 6X salt sodium citrate (SSC) is 1M. See Suggs *et al.*, *Developmental Biology Using Purified Genes* 683 (Brown and Fox, eds., 1981).

High stringency washing conditions for oligonucleotides are usually at a temperature of 0-5°C below the T_m of the oligonucleotide in 6X SSC, 0.1% SDS.

In another embodiment, related nucleic acid molecules comprise or consist of
20 a nucleotide sequence that is at least about 70 percent identical to the nucleotide sequence as shown in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22, or comprise or consist essentially of a nucleotide sequence encoding a polypeptide that is at least about 70 percent identical to the polypeptide as set forth in
25 any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. In preferred embodiments, the nucleotide sequences are about 75 percent, or about 80 percent, or about 85 percent, or about 90 percent, or about 95, 96, 97, 98, or 99 percent identical
30 to the nucleotide sequence as shown in any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22, or the nucleotide sequences encode a polypeptide that is about 75 percent, or about 80 percent, or about 85 percent, or about 90 percent, or about 95, 96, 97, 98, or 99 percent identical to the polypeptide sequence as set forth in

Conservative amino acid substitutions also encompass non-naturally occurring amino acid residues that are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics, and other reversed or inverted forms of amino acid moieties.

5 Naturally occurring residues may be divided into classes based on common side chain properties:

- 1) hydrophobic: norleucine, Met, Ala, Val, Leu, Ile;
- 2) neutral hydrophilic: Cys, Ser, Thr;
- 3) acidic: Asp, Glu;
- 10 4) basic: Asn, Gln, His, Lys, Arg;
- 5) residues that influence chain orientation: Gly, Pro; and
- 6) aromatic: Trp, Tyr, Phe.

For example, non-conservative substitutions may involve the exchange of a member of one of these classes for a member from another class. Such substituted
15 residues may be introduced into regions of the human LGR8 polypeptide that are homologous with non-human LGR8 polypeptides, or into the non-homologous regions of the molecule.

In making such changes, the hydropathic index of amino acids may be considered. Each amino acid has been assigned a hydropathic index on the basis of its
20 hydrophobicity and charge characteristics. The hydropathic indices are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (-0.4); threonine (-0.7); serine (-0.8); tryptophan (-0.9); tyrosine (-1.3); proline (-1.6); histidine (-3.2); glutamate (-3.5); glutamine (-3.5); aspartate (-3.5); asparagine (-3.5); lysine (-3.9); and arginine (-4.5).

25 The importance of the hydropathic amino acid index in conferring interactive biological function on a protein is generally understood in the art (Kyte *et al.*, 1982, *J. Mol. Biol.* 157:105-31). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, the
30 substitution of amino acids whose hydropathic indices are within ± 2 is preferred, those which are within ± 1 are particularly preferred, and those within ± 0.5 are even more particularly preferred.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically

Gly	Pro, Ala	Ala
His	Asn, Gln, Lys, Arg	Arg
Ile	Leu, Val, Met, Ala, Phe, Norleucine	Leu
Leu	Norleucine, Ile, Val, Met, Ala, Phe	Ile
Lys	Arg, 1,4 Diamino-butyric Acid, Gln, Asn	Arg
Met	Leu, Phe, Ile	Leu
Phe	Leu, Val, Ile, Ala, Tyr	Leu
Pro	Ala	Gly
Ser	Thr, Ala, Cys	Thr
Thr	Ser	Ser
Trp	Tyr, Phe	Tyr
Tyr	Trp, Phe, Thr, Ser	Phe
Val	Ile, Met, Leu, Phe, Ala, Norleucine	Leu

A skilled artisan will be able to determine suitable variants of the polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 using well-known techniques. For identifying suitable areas of the molecule that may be changed without destroying biological activity, one skilled in the art may target areas not believed to be important for activity. For example, when similar polypeptides with similar activities from the same species or from other species are known, one skilled in the art may compare the amino acid sequence of an LGR8 polypeptide to such similar polypeptides. With such a comparison, one can identify residues and portions of the molecules that are conserved among similar polypeptides. It will be appreciated that changes in areas of the LGR8 molecule that are not conserved relative to such similar polypeptides would be less likely to adversely affect the biological activity and/or structure of an LGR8 polypeptide. One skilled in

computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity greater than 40%, often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within the structure of a polypeptide or protein. See Holm *et al.*, 1999, *Nucleic Acids Res.* 27:244-47. It has been suggested that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate (Brenner *et al.*, 1997, *Curr. Opin. Struct. Biol.* 7:369-76).

Additional methods of predicting secondary structure include "threading" (Jones, 1997, *Curr. Opin. Struct. Biol.* 7:377-87; Sippl *et al.*, 1996, *Structure* 4:15-19), "profile analysis" (Bowie *et al.*, 1991, *Science*, 253:164-70; Gribskov *et al.*, 1990, *Methods Enzymol.* 183:146-59; Gribskov *et al.*, 1987, *Proc. Nat. Acad. Sci. U.S.A.* 84:4355-58), and "evolutionary linkage" (See Holm *et al.*, *supra*, and Brenner *et al.*, *supra*).

Preferred LGR8 polypeptide variants include glycosylation variants wherein the number and/or type of glycosylation sites have been altered compared to the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. In one embodiment, LGR8 polypeptide variants comprise a greater or a lesser number of N-linked glycosylation sites than the amino acid sequence set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. An N-linked glycosylation site is characterized by the sequence: Asn-X-Ser or Asn-X-Thr, wherein the amino acid residue designated as X may be any amino acid residue except proline. The substitution of amino acid residues to create this sequence provides a potential new site for the addition of an N-linked carbohydrate chain. Alternatively, substitutions that eliminate this sequence will remove an existing N-linked carbohydrate chain. Also provided is a rearrangement of N-linked carbohydrate chains wherein one or more N-linked glycosylation sites (typically those

SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23. Related nucleic acid molecules also comprise or consist of a nucleotide sequence encoding a polypeptide as set forth in
5 any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one modification selected from the group consisting of amino acid substitutions, amino acid insertions, amino acid deletions, carboxyl-terminal truncations, and
10 amino-terminal truncations and wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23.

15 In addition, the polypeptide comprising the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or other LGR8 polypeptide, may be fused to a homologous polypeptide to form a homodimer or to a
20 heterologous polypeptide to form a heterodimer. Heterologous peptides and polypeptides include, but are not limited to: an epitope to allow for the detection and/or isolation of an LGR8 fusion polypeptide; a transmembrane receptor protein or a portion thereof, such as an extracellular domain or a transmembrane and intracellular domain; a ligand or a portion thereof which binds to a transmembrane
25 receptor protein; an enzyme or portion thereof which is catalytically active; a polypeptide or peptide which promotes oligomerization, such as a leucine zipper domain; a polypeptide or peptide which increases stability, such as an immunoglobulin constant region; and a polypeptide which has a therapeutic activity different from the polypeptide comprising the amino acid sequence as set forth in any
30 of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or other LGR8 polypeptide.

IgG1	TNF receptor	septic shock	Fisher <i>et al.</i> , 1996, <i>N. Engl. J. Med.</i> 334:1697-1702; Van Zee <i>et al.</i> , 1996, <i>J. Immunol.</i> 156:2221-30
IgG, IgA, IgM, or IgE (excluding the first domain)	TNF receptor	inflammation, autoimmune disorders	U.S. Patent No. 5,808,029
IgG1	CD4 receptor	AIDS	Capon <i>et al.</i> , 1989, <i>Nature</i> 337: 525-31
IgG1, IgG3	N-terminus of IL-2	anti-cancer, antiviral	Harvill <i>et al.</i> , 1995, <i>Immunotech.</i> 1:95-105
IgG1	C-terminus of OPG	osteoarthritis; bone density	WO 97/23614
IgG1	N-terminus of leptin	anti-obesity	PCT/US 97/23183, filed December 11, 1997
Human Ig C γ 1	CTLA-4	autoimmune disorders	Linsley, 1991, <i>J. Exp. Med.</i> , 174:561-69

In one example, a human IgG hinge, CH2, and CH3 region may be fused at either the amino-terminus or carboxyl-terminus of the LGR8 polypeptides using methods known to the skilled artisan. In another example, a human IgG hinge, CH2, and CH3 region may be fused at either the amino-terminus or carboxyl-terminus of an LGR8 polypeptide fragment (*e.g.*, the predicted extracellular portion of LGR8 polypeptide).

The resulting LGR8 fusion polypeptide may be purified by use of a Protein A affinity column. Peptides and proteins fused to an Fc region have been found to exhibit a substantially greater half-life *in vivo* than the unfused counterpart. Also, a fusion to an Fc region allows for dimerization/multimerization of the fusion polypeptide. The Fc region may be a naturally occurring Fc region, or may be altered to improve certain qualities, such as therapeutic qualities, circulation time, or reduced aggregation.

Identity and similarity of related nucleic acid molecules and polypeptides are readily calculated by known methods. Such methods include, but are not limited to those described in *Computational Molecular Biology* (A.M. Lesk, ed., Oxford University Press 1988); *Biocomputing: Informatics and Genome Projects* (D.W. Smith, ed., Academic Press 1993); *Computer Analysis of Sequence Data* (Part 1, A.M. Griffin and H.G. Griffin, eds., Humana Press 1994); G. von Heinle, *Sequence Analysis in Molecular Biology* (Academic Press 1987); *Sequence Analysis Primer* (M.

Algorithm: Needleman and Wunsch, 1970, *J. Mol. Biol.* 48:443-53;

Comparison matrix: BLOSUM 62 (Henikoff *et al.*, *supra*);

Gap Penalty: 12

5 Gap Length Penalty: 4

Threshold of Similarity: 0

The GAP program is useful with the above parameters. The aforementioned parameters are the default parameters for polypeptide comparisons (along with no
10 penalty for end gaps) using the GAP algorithm.

Preferred parameters for nucleic acid molecule sequence comparison include the following:

Algorithm: Needleman and Wunsch, *supra*;

15 Comparison matrix: matches = +10, mismatch = 0

Gap Penalty: 50

Gap Length Penalty: 3

The GAP program is also useful with the above parameters. The aforementioned
20 parameters are the default parameters for nucleic acid molecule comparisons.

Other exemplary algorithms, gap opening penalties, gap extension penalties, comparison matrices, and thresholds of similarity may be used, including those set forth in the Program Manual, Wisconsin Package, Version 9, September, 1997. The particular choices to be made will be apparent to those of skill in the art and will
25 depend on the specific comparison to be made, such as DNA-to-DNA, protein-to-protein, protein-to-DNA; and additionally, whether the comparison is between given pairs of sequences (in which case GAP or BestFit are generally preferred) or between one sequence and a large database of sequences (in which case FASTA or BLASTA are preferred).

30

Nucleic Acid Molecules

The nucleic acid molecules encoding a polypeptide comprising the amino acid sequence of an LGR8 polypeptide can readily be obtained in a variety of ways

introducing the expression vector into an appropriate host, the encoded LGR8 polypeptide may be produced in large amounts.

Another method for obtaining a suitable nucleic acid sequence is the polymerase chain reaction (PCR). In this method, cDNA is prepared from poly(A)+RNA or total RNA using the enzyme reverse transcriptase. Two primers, typically complementary to two separate regions of cDNA encoding the amino acid sequence of an LGR8 polypeptide, are then added to the cDNA along with a polymerase such as *Taq* polymerase, and the polymerase amplifies the cDNA region between the two primers.

Another means of preparing a nucleic acid molecule encoding the amino acid sequence of an LGR8 polypeptide is chemical synthesis using methods well known to the skilled artisan such as those described by Engels *et al.*, 1989, *Angew. Chem. Intl. Ed.* 28:716-34. These methods include, *inter alia*, the phosphotriester, phosphoramidite, and H-phosphonate methods for nucleic acid synthesis. A preferred method for such chemical synthesis is polymer-supported synthesis using standard phosphoramidite chemistry. Typically, the DNA encoding the amino acid sequence of an LGR8 polypeptide will be several hundred nucleotides in length. Nucleic acids larger than about 100 nucleotides can be synthesized as several fragments using these methods. The fragments can then be ligated together to form the full-length nucleotide sequence of an LGR8 gene. Usually, the DNA fragment encoding the amino-terminus of the polypeptide will have an ATG, which encodes a methionine residue. This methionine may or may not be present on the mature form of the LGR8 polypeptide, depending on whether the polypeptide produced in the host cell is designed to be secreted from that cell. Other methods known to the skilled artisan may be used as well.

In certain embodiments, nucleic acid variants contain codons which have been altered for optimal expression of an LGR8 polypeptide in a given host cell. Particular codon alterations will depend upon the LGR8 polypeptide and host cell selected for expression. Such "codon optimization" can be carried out by a variety of methods, for example, by selecting codons which are preferred for use in highly expressed genes in a given host cell. Computer algorithms which incorporate codon frequency tables such as "Eco_high.Cod" for codon preference of highly expressed bacterial genes may be used and are provided by the University of Wisconsin Package Version 9.0 (Genetics Computer Group, Madison, WI). Other useful codon frequency tables

to be expressed, and a selectable marker element. Each of these sequences is discussed below.

Optionally, the vector may contain a "tag"-encoding sequence, *i.e.*, an oligonucleotide molecule located at the 5' or 3' end of the LGR8 polypeptide coding sequence; the oligonucleotide sequence encodes polyHis (such as hexaHis), or another "tag" such as FLAG, HA (hemagglutinin influenza virus), or *myc* for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification of the LGR8 polypeptide from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified LGR8 polypeptide by various means such as using certain peptidases for cleavage.

Flanking sequences may be homologous (*i.e.*, from the same species and/or strain as the host cell), heterologous (*i.e.*, from a species other than the host cell species or strain), hybrid (*i.e.*, a combination of flanking sequences from more than one source), or synthetic, or the flanking sequences may be native sequences that normally function to regulate LGR8 polypeptide expression. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors of this invention may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein – other than the LGR8 gene flanking sequences – will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Where all or only a portion of the flanking sequence is known, it may be obtained using PCR and/or by screening a genomic library with a suitable oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example,

Other selection genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are in greater demand for the production of a protein critical for growth are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable
5 selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and thymidine kinase. The mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selection gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in
10 the medium is successively changed, thereby leading to the amplification of both the selection gene and the DNA that encodes an LGR8 polypeptide. As a result, increased quantities of LGR8 polypeptide are synthesized from the amplified DNA.

A ribosome binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak
15 sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of an LGR8 polypeptide to be expressed. The Shine-Dalgarno sequence is varied but is typically a polypurine (*i.e.*, having a high A-G content). Many Shine-Dalgarno sequences have been identified, each of which can be readily synthesized using methods set forth herein and used in a prokaryotic vector.

20 A leader, or signal, sequence may be used to direct an LGR8 polypeptide out of the host cell. Typically, a nucleotide sequence encoding the signal sequence is positioned in the coding region of an LGR8 nucleic acid molecule, or directly at the 5' end of an LGR8 polypeptide coding region. Many signal sequences have been identified, and any of those that are functional in the selected host cell may be used in
25 conjunction with an LGR8 nucleic acid molecule. Therefore, a signal sequence may be homologous (naturally occurring) or heterologous to the LGR8 nucleic acid molecule. Additionally, a signal sequence may be chemically synthesized using methods described herein. In most cases, the secretion of an LGR8 polypeptide from the host cell via the presence of a signal peptide will result in the removal of the
30 signal peptide from the secreted LGR8 polypeptide. The signal sequence may be a component of the vector, or it may be a part of an LGR8 nucleic acid molecule that is inserted into the vector.

Included within the scope of this invention is the use of either a nucleotide sequence encoding a native LGR8 polypeptide signal sequence joined to an LGR8

not interrupt the coding sequence. Any intron from any source, including viral, prokaryotic and eukaryotic (plant or animal) organisms, may be used to practice this invention, provided that it is compatible with the host cell into which it is inserted. Also included herein are synthetic introns. Optionally, more than one intron may be used in the vector.

The expression and cloning vectors of the present invention will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding the LGR8 polypeptide. Promoters are untranscribed sequences located upstream (*i.e.*, 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control the transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, initiate continual gene product production; that is, there is little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding LGR8 polypeptide by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector. The native LGR8 promoter sequence may be used to direct amplification and/or expression of an LGR8 nucleic acid molecule. A heterologous promoter is preferred, however, if it permits greater transcription and higher yields of the expressed protein as compared to the native promoter, and if it is compatible with the host cell system that has been selected for use.

Promoters suitable for use with prokaryotic hosts include the beta-lactamase and lactose promoter systems; alkaline phosphatase; a tryptophan (*trp*) promoter system; and hybrid promoters such as the *tac* promoter. Other known bacterial promoters are also suitable. Their sequences have been published, thereby enabling one skilled in the art to ligate them to the desired DNA sequence, using linkers or adapters as needed to supply any useful restriction sites.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus,

gonadotropic releasing hormone gene control region which is active in the hypothalamus (Mason *et al.*, 1986, *Science* 234:1372-78).

An enhancer sequence may be inserted into the vector to increase the transcription of a DNA encoding an LGR8 polypeptide of the present invention by
5 higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent. They have been found 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (*e.g.*, globin, elastase, albumin, alpha-feto-protein and insulin). Typically,
10 however, an enhancer from a virus will be used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be spliced into the vector at a position 5' or 3' to an LGR8 nucleic acid molecule, it is typically located at a site 5' from the promoter.

15 Expression vectors of the invention may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking
20 sequences are well known to one skilled in the art.

Preferred vectors for practicing this invention are those that are compatible with bacterial, insect, and mammalian host cells. Such vectors include, *inter alia*, pCRII, pCR3, and pcDNA3.1 (Invitrogen, San Diego, CA), pBSII (Stratagene, La Jolla, CA), pET15 (Novagen, Madison, WI), pGEX (Pharmacia Biotech, Piscataway,
25 NJ), pEGFP-N2 (Clontech, Palo Alto, CA), pETL (BlueBacII, Invitrogen), pDSR-alpha (PCT Pub. No. WO 90/14363) and pFastBacDual (Gibco-BRL, Grand Island, NY).

Additional suitable vectors include, but are not limited to, cosmids, plasmids, or modified viruses, but it will be appreciated that the vector system must be
30 compatible with the selected host cell. Such vectors include, but are not limited to plasmids such as Bluescript[®] plasmid derivatives (a high copy number ColE1-based phagemid; Stratagene Cloning Systems, La Jolla CA), PCR cloning plasmids designed for cloning Taq-amplified PCR products (*e.g.*, TOPO[™] TA Cloning[®] Kit

may contain a dominantly acting selection gene. Other suitable mammalian cell lines include but are not limited to, mouse neuroblastoma N2A cells, HeLa, mouse L-929 cells, 3T3 lines derived from Swiss, Balb-c or NIH mice, BHK or HaK hamster cell lines. Each of these cell lines is known by and available to those skilled in the art of protein expression.

Similarly useful as host cells suitable for the present invention are bacterial cells. For example, the various strains of *E. coli* (e.g., HB101, DH5 α , DH10, and MC1061) are well-known as host cells in the field of biotechnology. Various strains of *B. subtilis*, *Pseudomonas spp.*, other *Bacillus spp.*, *Streptomyces spp.*, and the like may also be employed in this method.

Many strains of yeast cells known to those skilled in the art are also available as host cells for the expression of the polypeptides of the present invention. Preferred yeast cells include, for example, *Saccharomyces cerevisiae* and *Pichia pastoris*.

Additionally, where desired, insect cell systems may be utilized in the methods of the present invention. Such systems are described, for example, in Kitts *et al.*, 1993, *Biotechniques*, 14:810-17; Lucklow, 1993, *Curr. Opin. Biotechnol.* 4:564-72; and Lucklow *et al.*, 1993, *J. Virol.*, 67:4566-79. Preferred insect cells are Sf-9 and Hi5 (Invitrogen).

One may also use transgenic animals to express glycosylated LGR8 polypeptides. For example, one may use a transgenic milk-producing animal (a cow or goat, for example) and obtain the present glycosylated polypeptide in the animal milk. One may also use plants to produce LGR8 polypeptides, however, in general, the glycosylation occurring in plants is different from that produced in mammalian cells, and may result in a glycosylated product which is not suitable for human therapeutic use.

Polypeptide Production

Host cells comprising an LGR8 polypeptide expression vector may be cultured using standard media well known to the skilled artisan. The media will usually contain all nutrients necessary for the growth and survival of the cells. Suitable media for culturing *E. coli* cells include, for example, Luria Broth (LB) and/or Terrific Broth (TB). Suitable media for culturing eukaryotic cells include Roswell Park Memorial Institute medium 1640 (RPMI 1640), Minimal Essential Medium (MEM) and/or Dulbecco's Modified Eagle Medium (DMEM), all of which

LGR8 polypeptide can then be analyzed using gel electrophoresis, immunoprecipitation, or the like. If it is desired to isolate the LGR8 polypeptide, isolation may be accomplished using standard methods such as those described herein and in Marston *et al.*, 1990, *Meth. Enz.*, 182:264-75.

5 In some cases, an LGR8 polypeptide may not be biologically active upon isolation. Various methods for "refolding" or converting the polypeptide to its tertiary structure and generating disulfide linkages can be used to restore biological activity. Such methods include exposing the solubilized polypeptide to a pH usually above 7 and in the presence of a particular concentration of a chaotrope. The
10 selection of chaotrope is very similar to the choices used for inclusion body solubilization, but usually the chaotrope is used at a lower concentration and is not necessarily the same as chaotropes used for the solubilization. In most cases the refolding/oxidation solution will also contain a reducing agent or the reducing agent plus its oxidized form in a specific ratio to generate a particular redox potential
15 allowing for disulfide shuffling to occur in the formation of the protein's cysteine bridges. Some of the commonly used redox couples include cysteine/cystamine, glutathione (GSH)/dithiobis GSH, cupric chloride, dithiothreitol(DTT)/dithiane DTT, and 2-2-mercaptoethanol(bME)/dithio-b(ME). In many instances, a cosolvent may be used or may be needed to increase the efficiency of the refolding, and the more
20 common reagents used for this purpose include glycerol, polyethylene glycol of various molecular weights, arginine and the like.

If inclusion bodies are not formed to a significant degree upon expression of an LGR8 polypeptide, then the polypeptide will be found primarily in the supernatant after centrifugation of the cell homogenate. The polypeptide may be further isolated
25 from the supernatant using methods such as those described herein.

The purification of an LGR8 polypeptide from solution can be accomplished using a variety of techniques. If the polypeptide has been synthesized such that it contains a tag such as Hexahistidine (LGR8 polypeptide/hexaHis) or other small peptide such as FLAG (Eastman Kodak Co., New Haven, CT) or *myc* (Invitrogen) at
30 either its carboxyl- or amino-terminus, it may be purified in a one-step process by passing the solution through an affinity column where the column matrix has a high affinity for the tag.

For example, polyhistidine binds with great affinity and specificity to nickel. Thus, an affinity column of nickel (such as the Qiagen[®] nickel columns) can be used

an mRNA and its encoded peptide. *See also*, Roberts, 1999, *Curr. Opin. Chem. Biol.* 3:268-73. Additionally, U.S. Patent No. 5,824,469 describes methods for obtaining oligonucleotides capable of carrying out a specific biological function. The procedure involves generating a heterogeneous pool of oligonucleotides, each having a 5' randomized sequence, a central preselected sequence, and a 3' randomized sequence. The resulting heterogeneous pool is introduced into a population of cells that do not exhibit the desired biological function. Subpopulations of the cells are then screened for those that exhibit a predetermined biological function. From that subpopulation, oligonucleotides capable of carrying out the desired biological function are isolated.

U.S. Patent Nos. 5,763,192; 5,814,476; 5,723,323; and 5,817,483 describe processes for producing peptides or polypeptides. This is done by producing stochastic genes or fragments thereof, and then introducing these genes into host cells which produce one or more proteins encoded by the stochastic genes. The host cells are then screened to identify those clones producing peptides or polypeptides having the desired activity.

Another method for producing peptides or polypeptides is described in PCT/US98/20094 (WO99/15650) filed by Athersys, Inc. Known as "Random Activation of Gene Expression for Gene Discovery" (RAGE-GD), the process involves the activation of endogenous gene expression or over-expression of a gene by *in situ* recombination methods. For example, expression of an endogenous gene is activated or increased by integrating a regulatory sequence into the target cell that is capable of activating expression of the gene by non-homologous or illegitimate recombination. The target DNA is first subjected to radiation, and a genetic promoter inserted. The promoter eventually locates a break at the front of a gene, initiating transcription of the gene. This results in expression of the desired peptide or polypeptide.

It will be appreciated that these methods can also be used to create comprehensive LGR8 polypeptide expression libraries, which can subsequently be used for high throughput phenotypic screening in a variety of assays, such as biochemical assays, cellular assays, and whole organism assays (e.g., plant, mouse, etc.).

Synthesis

monoclonal antibodies include the hybridoma methods of Kohler *et al.*, 1975, *Nature* 256:495-97 and the human B-cell hybridoma method (Kozbor, 1984, *J. Immunol.* 133:3001; Brodeur *et al.*, *Monoclonal Antibody Production Techniques and Applications* 51-63 (Marcel Dekker, Inc., 1987). Also provided by the invention are
5 hybridoma cell lines that produce monoclonal antibodies reactive with LGR8 polypeptides.

Monoclonal antibodies of the invention may be modified for use as therapeutics. One embodiment is a "chimeric" antibody in which a portion of the heavy (H) and/or light (L) chain is identical with or homologous to a corresponding
10 sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. Also included are fragments of such antibodies, so long as they exhibit the desired biological activity. See U.S.
15 Patent No. 4,816,567; Morrison *et al.*, 1985, *Proc. Natl. Acad. Sci.* 81:6851-55.

In another embodiment, a monoclonal antibody of the invention is a "humanized" antibody. Methods for humanizing non-human antibodies are well known in the art. See U.S. Patent Nos. 5,585,089 and 5,693,762. Generally, a humanized antibody has one or more amino acid residues introduced into it from a
20 source that is non-human. Humanization can be performed, for example, using methods described in the art (Jones *et al.*, 1986, *Nature* 321:522-25; Riechmann *et al.*, 1998, *Nature* 332:323-27; Verhoeven *et al.*, 1988, *Science* 239:1534-36), by substituting at least a portion of a rodent complementarity-determining region for the corresponding regions of a human antibody.

Also encompassed by the invention are human antibodies that bind LGR8 polypeptides. Using transgenic animals (*e.g.*, mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production such antibodies are produced by immunization with an LGR8 polypeptide antigen (*i.e.*, having at least 6 contiguous amino acids), optionally conjugated to a
25 carrier. See, *e.g.*, Jakobovits *et al.*, 1993, *Proc. Natl. Acad. Sci.* 90:2551-55; Jakobovits *et al.*, 1993, *Nature* 362:255-58; Bruggermann *et al.*, 1993, *Year in Immuno.* 7:33. In one method, such transgenic animals are produced by incapacitating the endogenous loci encoding the heavy and light immunoglobulin chains therein, and inserting loci encoding human heavy and light chain proteins into
30

the detectable moiety may be a radioisotope, such as ^3H , ^{14}C , ^{32}P , ^{35}S , ^{125}I , ^{99}Tc , ^{111}In , or ^{67}Ga ; a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin; or an enzyme, such as alkaline phosphatase, β -galactosidase, or horseradish peroxidase (Bayer, *et al.*, 1990, *Meth. Enz.* 184:138-5 63).

Competitive binding assays rely on the ability of a labeled standard (*e.g.*, an LGR8 polypeptide, or an immunologically reactive portion thereof) to compete with the test sample analyte (an LGR8 polypeptide) for binding with a limited amount of anti-LGR8 antibody. The amount of an LGR8 polypeptide in the test sample is 10 inversely proportional to the amount of standard that becomes bound to the antibodies. To facilitate determining the amount of standard that becomes bound, the antibodies typically are insolubilized before or after the competition, so that the standard and analyte that are bound to the antibodies may conveniently be separated from the standard and analyte that remain unbound.

15 Sandwich assays typically involve the use of two antibodies, each capable of binding to a different immunogenic portion, or epitope, of the protein to be detected and/or quantitated. In a sandwich assay, the test sample analyte is typically bound by a first antibody that is immobilized on a solid support, and thereafter a second antibody binds to the analyte, thus forming an insoluble three-part complex. *See, e.g.*, 20 U.S. Patent No. 4,376,110. The second antibody may itself be labeled with a detectable moiety (direct sandwich assays) or may be measured using an anti-immunoglobulin antibody that is labeled with a detectable moiety (indirect sandwich assays). For example, one type of sandwich assay is an enzyme-linked immunosorbent assay (ELISA), in which case the detectable moiety is an enzyme.

25 The selective binding agents, including anti-LGR8 antibodies, are also useful for *in vivo* imaging. An antibody labeled with a detectable moiety may be administered to an animal, preferably into the bloodstream, and the presence and location of the labeled antibody in the host assayed. The antibody may be labeled with any moiety that is detectable in an animal, whether by nuclear magnetic 30 resonance, radiology, or other detection means known in the art.

Selective binding agents of the invention, including antibodies, may be used as therapeutics. These therapeutic agents are generally agonists or antagonists, in that they either enhance or reduce, respectively, at least one of the biological activities of an LGR8 polypeptide. In one embodiment, antagonist antibodies of the invention are

of populations and generation of surrogate markers for clinical trials; and enhancing related LGR8 polypeptide small molecule drug discovery by aiding in the identification of selective compounds in high throughput screens.

5 Chemical Derivatives

Chemically modified derivatives of LGR8 polypeptides may be prepared by one skilled in the art, given the disclosures described herein. LGR8 polypeptide derivatives are modified in a manner that is different -- either in the type or location of the molecules naturally attached to the polypeptide. Derivatives may include
10 molecules formed by the deletion of one or more naturally-attached chemical groups. The polypeptide comprising the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or other LGR8 polypeptide, may be
15 modified by the covalent attachment of one or more polymers. For example, the polymer selected is typically water-soluble so that the protein to which it is attached does not precipitate in an aqueous environment, such as a physiological environment. Included within the scope of suitable polymers is a mixture of polymers. Preferably, for therapeutic use of the end-product preparation, the polymer will be
20 pharmaceutically acceptable.

The polymers each may be of any molecular weight and may be branched or unbranched. The polymers each typically have an average molecular weight of between about 2 kDa to about 100 kDa (the term "about" indicating that in preparations of a water-soluble polymer, some molecules will weigh more, some less,
25 than the stated molecular weight). The average molecular weight of each polymer is preferably between about 5 kDa and about 50 kDa, more preferably between about 12 kDa and about 40 kDa and most preferably between about 20 kDa and about 35 kDa.

Suitable water-soluble polymers or mixtures thereof include, but are not limited to, N-linked or O-linked carbohydrates, sugars, phosphates, polyethylene glycol (PEG) (including the forms of PEG that have been used to derivatize proteins,
30 including mono-(C₁-C₁₀), alkoxy-, or aryloxy-polyethylene glycol), monomethoxy-polyethylene glycol, dextran (such as low molecular weight dextran of, for example, about 6 kD), cellulose, or other carbohydrate based polymers, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene

(TNP) and the resulting conjugates precipitated with anti-DNP or anti-TNP-IgM to form decameric conjugates with a valency of 10.

Generally, conditions that may be alleviated or modulated by the administration of the present LGR8 polypeptide derivatives include those described
5 herein for LGR8 polypeptides. However, the LGR8 polypeptide derivatives disclosed herein may have additional activities, enhanced or reduced biological activity, or other characteristics, such as increased or decreased half-life, as compared to the non-derivatized molecules.

10 Genetically Engineered Non-Human Animals

Additionally included within the scope of the present invention are non-human animals such as mice, rats, or other rodents; rabbits, goats, sheep, or other farm animals, in which the genes encoding native LGR8 polypeptide have been disrupted (*i.e.*, "knocked out") such that the level of expression of LGR8 polypeptide is
15 significantly decreased or completely abolished. Such animals may be prepared using techniques and methods such as those described in U.S. Patent No. 5,557,032.

The present invention further includes non-human animals such as mice, rats, or other rodents; rabbits, goats, sheep, or other farm animals, in which either the native form of an LGR8 gene for that animal or a heterologous LGR8 gene is over-
20 expressed by the animal, thereby creating a "transgenic" animal. Such transgenic animals may be prepared using well known methods such as those described in U.S. Patent No 5,489,743 and PCT Pub. No. WO 94/28122.

The present invention further includes non-human animals in which the promoter for one or more of the LGR8 polypeptides of the present invention is either
25 activated or inactivated (*e.g.*, by using homologous recombination methods) to alter the level of expression of one or more of the native LGR8 polypeptides.

These non-human animals may be used for drug candidate screening. In such screening, the impact of a drug candidate on the animal may be measured. For example, drug candidates may decrease or increase the expression of the LGR8 gene.
30 In certain embodiments, the amount of LGR8 polypeptide that is produced may be measured after the exposure of the animal to the drug candidate. Additionally, in certain embodiments, one may detect the actual impact of the drug candidate on the animal. For example, over-expression of a particular gene may result in, or be associated with, a disease or pathological condition. In such cases, one may test a

sequences which direct or control the expression of LGR8 polypeptide, and which act as anti-sense regulators of expression.

Once a test molecule has been identified as interacting with an LGR8 polypeptide, the molecule may be further evaluated for its ability to increase or decrease LGR8 polypeptide activity. The measurement of the interaction of a test molecule with LGR8 polypeptide may be carried out in several formats, including cell-based binding assays, membrane binding assays, solution-phase assays, and immunoassays. In general, a test molecule is incubated with an LGR8 polypeptide for a specified period of time, and LGR8 polypeptide activity is determined by one or more assays for measuring biological activity.

The interaction of test molecules with LGR8 polypeptides may also be assayed directly using polyclonal or monoclonal antibodies in an immunoassay. Alternatively, modified forms of LGR8 polypeptides containing epitope tags as described herein may be used in solution and immunoassays.

In the event that LGR8 polypeptides display biological activity through an interaction with a binding partner (*e.g.*, a receptor or a ligand), a variety of *in vitro* assays may be used to measure the binding of an LGR8 polypeptide to the corresponding binding partner (such as a selective binding agent, receptor, or ligand). These assays may be used to screen test molecules for their ability to increase or decrease the rate and/or the extent of binding of an LGR8 polypeptide to its binding partner. In one assay, an LGR8 polypeptide is immobilized in the wells of a microtiter plate. Radiolabeled LGR8 polypeptide binding partner (for example, iodinated LGR8 polypeptide binding partner) and a test molecule can then be added either one at a time (in either order) or simultaneously to the wells. After incubation, the wells can be washed and counted for radioactivity, using a scintillation counter, to determine the extent to which the binding partner bound to the LGR8 polypeptide. Typically, a molecule will be tested over a range of concentrations, and a series of control wells lacking one or more elements of the test assays can be used for accuracy in the evaluation of the results. An alternative to this method involves reversing the "positions" of the proteins, *i.e.*, immobilizing LGR8 polypeptide binding partner to the microtiter plate wells, incubating with the test molecule and radiolabeled LGR8 polypeptide, and determining the extent of LGR8 polypeptide binding. *See, e.g., Current Protocols in Molecular Biology*, chap. 18 (Ausubel *et al.*, eds., Green Publishers Inc. and Wiley and Sons 1995).

an LGR8 polypeptide and an LGR8 polypeptide binding partner. In these cases, the assays set forth herein can be readily modified by adding such additional test compound(s) either simultaneously with, or subsequent to, the first test compound. The remainder of the steps in the assay are as set forth herein.

5 *In vitro* assays such as those described herein may be used advantageously to screen large numbers of compounds for an effect on the formation of a complex between an LGR8 polypeptide and LGR8 polypeptide binding partner. The assays may be automated to screen compounds generated in phage display, synthetic peptide, and chemical synthesis libraries.

10 Compounds which increase or decrease the formation of a complex between an LGR8 polypeptide and an LGR8 polypeptide binding partner may also be screened in cell culture using cells and cell lines expressing either LGR8 polypeptide or LGR8 polypeptide binding partner. Cells and cell lines may be obtained from any mammal, but preferably will be from human or other primate, canine, or rodent sources. The
15 binding of an LGR8 polypeptide to cells expressing LGR8 polypeptide binding partner at the surface is evaluated in the presence or absence of test molecules, and the extent of binding may be determined by, for example, flow cytometry using a biotinylated antibody to an LGR8 polypeptide binding partner. Cell culture assays can be used advantageously to further evaluate compounds that score positive in
20 protein binding assays described herein.

Cell cultures can also be used to screen the impact of a drug candidate. For example, drug candidates may decrease or increase the expression of the LGR8 gene. In certain embodiments, the amount of LGR8 polypeptide or an LGR8 polypeptide fragment that is produced may be measured after exposure of the cell culture to the
25 drug candidate. In certain embodiments, one may detect the actual impact of the drug candidate on the cell culture. For example, the over-expression of a particular gene may have a particular impact on the cell culture. In such cases, one may test a drug candidate's ability to increase or decrease the expression of the gene or its ability to prevent or inhibit a particular impact on the cell culture. In other examples, the
30 production of a particular metabolic product such as a fragment of a polypeptide, may result in, or be associated with, a disease or pathological condition. In such cases, one may test a drug candidate's ability to decrease the production of such a metabolic product in a cell culture.

In accordance with certain embodiments of the invention, it may be useful to be able to determine the source of a certain cell type associated with an LGR8 polypeptide. For example, it may be useful to determine the origin of a disease or pathological condition as an aid in selecting an appropriate therapy. In certain
5 embodiments, nucleic acids encoding an LGR8 polypeptide can be used as a probe to identify cells described herein by screening the nucleic acids of the cells with such a probe. In other embodiments, one may use anti-LGR8 polypeptide antibodies to test for the presence of LGR8 polypeptide in cells, and thus, determine if such cells are of the types described herein.

10

LGR8 Polypeptide Compositions and Administration

Therapeutic compositions are within the scope of the present invention. Such LGR8 polypeptide pharmaceutical compositions may comprise a therapeutically effective amount of an LGR8 polypeptide or an LGR8 nucleic acid molecule in
15 admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration. Pharmaceutical compositions may comprise a therapeutically effective amount of one or more LGR8 polypeptide selective binding agents in admixture with a pharmaceutically or physiologically acceptable formulation agent selected for suitability with the mode of administration.

20

Acceptable formulation materials preferably are nontoxic to recipients at the dosages and concentrations employed.

The pharmaceutical composition may contain formulation materials for modifying, maintaining, or preserving, for example, the pH, osmolarity, viscosity, clarity, color, isotonicity, odor, sterility, stability, rate of dissolution or release,
25 adsorption, or penetration of the composition. Suitable formulation materials include, but are not limited to, amino acids (such as glycine, glutamine, asparagine, arginine, or lysine), antimicrobials, antioxidants (such as ascorbic acid, sodium sulfite, or sodium hydrogen-sulfite), buffers (such as borate, bicarbonate, Tris-HCl, citrates, phosphates, or other organic acids), bulking agents (such as mannitol or glycine),
30 chelating agents (such as ethylenediamine tetraacetic acid (EDTA)), complexing agents (such as caffeine, polyvinylpyrrolidone, beta-cyclodextrin, or hydroxypropyl-beta-cyclodextrin), fillers, monosaccharides, disaccharides, and other carbohydrates (such as glucose, mannose, or dextrans), proteins (such as serum albumin, gelatin, or immunoglobulins), coloring, flavoring and diluting agents, emulsifying agents,

pharmaceutically acceptable compositions is within the skill of the art.

The formulation components are present in concentrations that are acceptable to the site of administration. For example, buffers are used to maintain the composition at physiological pH or at a slightly lower pH, typically within a pH range of from about 5 to about 8.

When parenteral administration is contemplated, the therapeutic compositions for use in this invention may be in the form of a pyrogen-free, parenterally acceptable, aqueous solution comprising the desired LGR8 molecule in a pharmaceutically acceptable vehicle. A particularly suitable vehicle for parenteral injection is sterile distilled water in which an LGR8 molecule is formulated as a sterile, isotonic solution, properly preserved. Yet another preparation can involve the formulation of the desired molecule with an agent, such as injectable microspheres, bio-erodible particles, polymeric compounds (such as polylactic acid or polyglycolic acid), beads, or liposomes, that provides for the controlled or sustained release of the product which may then be delivered via a depot injection. Hyaluronic acid may also be used, and this may have the effect of promoting sustained duration in the circulation. Other suitable means for the introduction of the desired molecule include implantable drug delivery devices.

In one embodiment, a pharmaceutical composition may be formulated for inhalation. For example, LGR8 polypeptide may be formulated as a dry powder for inhalation. LGR8 polypeptide or nucleic acid molecule inhalation solutions may also be formulated with a propellant for aerosol delivery. In yet another embodiment, solutions may be nebulized. Pulmonary administration is further described in PCT Pub. No. WO 94/20069, which describes the pulmonary delivery of chemically modified proteins.

It is also contemplated that certain formulations may be administered orally. In one embodiment of the present invention, LGR8 polypeptides that are administered in this fashion can be formulated with or without those carriers customarily used in the compounding of solid dosage forms such as tablets and capsules. For example, a capsule may be designed to release the active portion of the formulation at the point in the gastrointestinal tract when bioavailability is maximized and pre-systemic degradation is minimized. Additional agents can be included to facilitate absorption of the LGR8 polypeptide. Diluents, flavorings, low melting point waxes, vegetable

lyophilized form or in a solution. In addition, parenteral compositions generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

Once the pharmaceutical composition has been formulated, it may be stored in sterile vials as a solution, suspension, gel, emulsion, solid, or as a dehydrated or lyophilized powder. Such formulations may be stored either in a ready-to-use form or in a form (*e.g.*, lyophilized) requiring reconstitution prior to administration.

In a specific embodiment, the present invention is directed to kits for producing a single-dose administration unit. The kits may each contain both a first container having a dried protein and a second container having an aqueous formulation. Also included within the scope of this invention are kits containing single and multi-chambered pre-filled syringes (*e.g.*, liquid syringes and lyosyringes).

The effective amount of an LGR8 pharmaceutical composition to be employed therapeutically will depend, for example, upon the therapeutic context and objectives. One skilled in the art will appreciate that the appropriate dosage levels for treatment will thus vary depending, in part, upon the molecule delivered, the indication for which the LGR8 molecule is being used, the route of administration, and the size (body weight, body surface, or organ size) and condition (the age and general health) of the patient. Accordingly, the clinician may titer the dosage and modify the route of administration to obtain the optimal therapeutic effect. A typical dosage may range from about 0.1 $\mu\text{g/kg}$ to up to about 100 mg/kg or more, depending on the factors mentioned above. In other embodiments, the dosage may range from 0.1 $\mu\text{g/kg}$ up to about 100 mg/kg; or 1 $\mu\text{g/kg}$ up to about 100 mg/kg; or 5 $\mu\text{g/kg}$ up to about 100 mg/kg.

The frequency of dosing will depend upon the pharmacokinetic parameters of the LGR8 molecule in the formulation being used. Typically, a clinician will administer the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Further refinement of the appropriate dosage is routinely made by those of ordinary skill in the art and is within the ambit of tasks routinely performed by them. Appropriate dosages may be ascertained through use of appropriate dose-response data.

polypeptides.

Homologous recombination is a technique originally developed for targeting genes to induce or correct mutations in transcriptionally active genes. Kucherlapati, 1989, *Prog. in Nucl. Acid Res. & Mol. Biol.* 36:301. The basic technique was developed as a method for introducing specific mutations into specific regions of the mammalian genome (Thomas *et al.*, 1986, *Cell* 44:419-28; Thomas and Capecchi, 1987, *Cell* 51:503-12; Doetschman *et al.*, 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:8583-87) or to correct specific mutations within defective genes (Doetschman *et al.*, 1987, *Nature* 330:576-78). Exemplary homologous recombination techniques are described in U.S. Patent No. 5,272,071; European Patent Nos. 9193051 and 505500; PCT/US90/07642, and PCT Pub No. WO 91/09955).

Through homologous recombination, the DNA sequence to be inserted into the genome can be directed to a specific region of the gene of interest by attaching it to targeting DNA. The targeting DNA is a nucleotide sequence that is complementary (homologous) to a region of the genomic DNA. Small pieces of targeting DNA that are complementary to a specific region of the genome are put in contact with the parental strand during the DNA replication process. It is a general property of DNA that has been inserted into a cell to hybridize, and therefore, recombine with other pieces of endogenous DNA through shared homologous regions. If this complementary strand is attached to an oligonucleotide that contains a mutation or a different sequence or an additional nucleotide, it too is incorporated into the newly synthesized strand as a result of the recombination. As a result of the proofreading function, it is possible for the new sequence of DNA to serve as the template. Thus, the transferred DNA is incorporated into the genome.

Attached to these pieces of targeting DNA are regions of DNA that may interact with or control the expression of an LGR8 polypeptide, *e.g.*, flanking sequences. For example, a promoter/enhancer element, a suppressor, or an exogenous transcription modulatory element is inserted in the genome of the intended host cell in proximity and orientation sufficient to influence the transcription of DNA encoding the desired LGR8 polypeptide. The control element controls a portion of the DNA present in the host cell genome. Thus, the expression of the desired LGR8 polypeptide may be achieved not by transfection of DNA that encodes the LGR8 gene itself, but rather by the use of targeting DNA (containing regions of homology with the endogenous gene of interest) coupled with DNA regulatory segments that provide

properly positioned in this plasmid, would integrate in such a manner as to create a new or modified transcriptional unit resulting in *de novo* or increased LGR8 polypeptide production from the cell's endogenous LGR8 gene.

5 A further method to use the cell line in which the site specific recombination sequence had been placed just upstream of the cell's endogenous genomic LGR8 polypeptide coding region is to use homologous recombination to introduce a second recombination site elsewhere in the cell line's genome. The appropriate recombinase enzyme is then introduced into the two-recombination-site cell line, causing a recombination event (deletion, inversion, and translocation) (Sauer, 1994, *Curr. Opin.*
10 *Biotechnol.*, 5:521-27; Sauer, 1993, *Methods Enzymol.*, 225:890-900) that would create a new or modified transcriptional unit resulting in *de novo* or increased LGR8 polypeptide production from the cell's endogenous LGR8 gene.

An additional approach for increasing, or causing, the expression of LGR8 polypeptide from a cell's endogenous LGR8 gene involves increasing, or causing, the
15 expression of a gene or genes (*e.g.*, transcription factors) and/or decreasing the expression of a gene or genes (*e.g.*, transcriptional repressors) in a manner which results in *de novo* or increased LGR8 polypeptide production from the cell's endogenous LGR8 gene. This method includes the introduction of a non-naturally occurring polypeptide (*e.g.*, a polypeptide comprising a site specific DNA binding
20 domain fused to a transcriptional factor domain) into the cell such that *de novo* or increased LGR8 polypeptide production from the cell's endogenous LGR8 gene results.

The present invention further relates to DNA constructs useful in the method of altering expression of a target gene. In certain embodiments, the exemplary DNA
25 constructs comprise: (a) one or more targeting sequences, (b) a regulatory sequence, (c) an exon, and (d) an unpaired splice-donor site. The targeting sequence in the DNA construct directs the integration of elements (a) - (d) into a target gene in a cell such that the elements (b) - (d) are operatively linked to sequences of the endogenous target gene. In another embodiment, the DNA constructs comprise: (a) one or more
30 targeting sequences, (b) a regulatory sequence, (c) an exon, (d) a splice-donor site, (e) an intron, and (f) a splice-acceptor site, wherein the targeting sequence directs the integration of elements (a) - (f) such that the elements of (b) - (f) are operatively linked to the endogenous gene. The targeting sequence is homologous to the preselected site in the cellular chromosomal DNA with which homologous

Alternatively, the patient's own cells, transformed to produce LGR8 polypeptides *ex vivo*, may be implanted directly into the patient without such encapsulation.

Techniques for the encapsulation of living cells are known in the art, and the preparation of the encapsulated cells and their implantation in patients may be routinely accomplished. For example, Baetge *et al.* (PCT Pub. No. WO 95/05452 and PCT/US94/09299) describe membrane capsules containing genetically engineered cells for the effective delivery of biologically active molecules. The capsules are biocompatible and are easily retrievable. The capsules encapsulate cells transfected with recombinant DNA molecules comprising DNA sequences coding for biologically active molecules operatively linked to promoters that are not subject to down-regulation *in vivo* upon implantation into a mammalian host. The devices provide for the delivery of the molecules from living cells to specific sites within a recipient. In addition, see U.S. Patent Nos. 4,892,538; 5,011,472; and 5,106,627. A system for encapsulating living cells is described in PCT Pub. No. WO 91/10425 (Aebischer *et al.*). See also, PCT Pub. No. WO 91/10470 (Aebischer *et al.*); Winn *et al.*, 1991, *Exper. Neurol.* 113:322-29; Aebischer *et al.*, 1991, *Exper. Neurol.* 111:269-75; and Tresco *et al.*, 1992, *ASAIO* 38:17-23.

In vivo and *in vitro* gene therapy delivery of LGR8 polypeptides is also envisioned. One example of a gene therapy technique is to use the LGR8 gene (either genomic DNA, cDNA, and/or synthetic DNA) encoding an LGR8 polypeptide that may be operably linked to a constitutive or inducible promoter to form a "gene therapy DNA construct." The promoter may be homologous or heterologous to the endogenous LGR8 gene, provided that it is active in the cell or tissue type into which the construct will be inserted. Other components of the gene therapy DNA construct may optionally include DNA molecules designed for site-specific integration (e.g., endogenous sequences useful for homologous recombination), tissue-specific promoters, enhancers or silencers, DNA molecules capable of providing a selective advantage over the parent cell, DNA molecules useful as labels to identify transformed cells, negative selection systems, cell specific binding agents (as, for example, for cell targeting), cell-specific internalization factors, transcription factors enhancing expression from a vector, and factors enabling vector production.

A gene therapy DNA construct can then be introduced into cells (either *ex vivo* or *in vivo*) using viral or non-viral vectors. One means for introducing the gene therapy DNA construct is by means of viral vectors as described herein. Certain

ecdysone-responsive gene). The ecdysone receptor includes a transactivation domain, DNA-binding domain, and ligand-binding domain to initiate transcription. The ecdysone system is further described in U.S. Patent No. 5,514,578 and PCT Pub. Nos. WO 97/38117, WO 96/37609, and WO 93/03162.

5 Another control means uses a positive tetracycline-controllable transactivator. This system involves a mutated tet repressor protein DNA-binding domain (mutated tet R-4 amino acid changes which resulted in a reverse tetracycline-regulated transactivator protein, *i.e.*, it binds to a tet operator in the presence of tetracycline) linked to a polypeptide which activates transcription. Such systems are described in
10 U.S. Patent Nos. 5,464,758, 5,650,298, and 5,654,168.

Additional expression control systems and nucleic acid constructs are described in U.S. Patent Nos. 5,741,679 and 5,834,186, to Innovir Laboratories Inc.

In vivo gene therapy may be accomplished by introducing the gene encoding LGR8 polypeptide into cells via local injection of an LGR8 nucleic acid molecule or
15 by other appropriate viral or non-viral delivery vectors. Hefti 1994, *Neurobiology* 25:1418-35. For example, a nucleic acid molecule encoding an LGR8 polypeptide may be contained in an adeno-associated virus (AAV) vector for delivery to the targeted cells (*see, e.g.*, Johnson, PCT Pub. No. WO 95/34670; PCT App. No. PCT/US95/07178). The recombinant AAV genome typically contains AAV inverted
20 terminal repeats flanking a DNA sequence encoding an LGR8 polypeptide operably linked to functional promoter and polyadenylation sequences.

Alternative suitable viral vectors include, but are not limited to, retrovirus, adenovirus, herpes simplex virus, lentivirus, hepatitis virus, parvovirus, papovavirus, poxvirus, alphavirus, coronavirus, rhabdovirus, paramyxovirus, and papilloma virus
25 vectors. U.S. Patent No. 5,672,344 describes an *in vivo* viral-mediated gene transfer system involving a recombinant neurotrophic HSV-1 vector. U.S. Patent No. 5,399,346 provides examples of a process for providing a patient with a therapeutic protein by the delivery of human cells that have been treated *in vitro* to insert a DNA segment encoding a therapeutic protein. Additional methods and materials for the
30 practice of gene therapy techniques are described in U.S. Patent Nos. 5,631,236 (involving adenoviral vectors), 5,672,510 (involving retroviral vectors), 5,635,399 (involving retroviral vectors expressing cytokines).

Nonviral delivery methods include, but are not limited to, liposome-mediated transfer, naked DNA delivery (direct injection), receptor-mediated transfer (ligand-

Gene therapy also can be used to decrease LGR8 polypeptide expression by modifying the nucleotide sequence of the endogenous promoter. Such modification is typically accomplished via homologous recombination methods. For example, a DNA molecule containing all or a portion of the promoter of the LGR8 gene selected for inactivation can be engineered to remove and/or replace pieces of the promoter that regulate transcription. For example, the TATA box and/or the binding site of a transcriptional activator of the promoter may be deleted using standard molecular biology techniques; such deletion can inhibit promoter activity thereby repressing the transcription of the corresponding LGR8 gene. The deletion of the TATA box or the transcription activator binding site in the promoter may be accomplished by generating a DNA construct comprising all or the relevant portion of the LGR8 polypeptide promoter (from the same or a related species as the LGR8 gene to be regulated) in which one or more of the TATA box and/or transcriptional activator binding site nucleotides are mutated via substitution, deletion and/or insertion of one or more nucleotides. As a result, the TATA box and/or activator binding site has decreased activity or is rendered completely inactive. This construct, which also will typically contain at least about 500 bases of DNA that correspond to the native (endogenous) 5' and 3' DNA sequences adjacent to the promoter segment that has been modified, may be introduced into the appropriate cells (either *ex vivo* or *in vivo*) either directly or via a viral vector as described herein. Typically, the integration of the construct into the genomic DNA of the cells will be via homologous recombination, where the 5' and 3' DNA sequences in the promoter construct can serve to help integrate the modified promoter region via hybridization to the endogenous chromosomal DNA.

25

Therapeutic Uses

LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof can be used to treat, diagnose, ameliorate, or prevent a number of diseases, disorders, or conditions, including those recited herein.

30

LGR8 polypeptide agonists and antagonists include those molecules which regulate LGR8 polypeptide activity and either increase or decrease at least one activity of the mature form of the LGR8 polypeptide. Agonists or antagonists may be co-factors, such as a protein, peptide, carbohydrate, lipid, or small molecular weight molecule, which interact with LGR8 polypeptide and thereby regulate its activity.

Since LGR8 polypeptide expression has been detected in the uterus, LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof may be useful in diagnosing or treating diseases and conditions affecting skeletal muscle. Examples of such diseases and conditions include, but are not limited to, miscarriage, endometriosis, uterine cancer, and female infertility. Other diseases and conditions associated with uterine development and function are encompassed within the scope of this invention.

Since LGR8 polypeptide expression has been detected in the adrenal gland, LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof may be useful in diagnosing or treating diseases and conditions affecting the adrenal gland. Examples of such diseases and conditions include, but are not limited to, Cushing's disease and Addison's disease. Other diseases and conditions associated with the development and function of the adrenal gland are encompassed within the scope of this invention.

Since LGR8 polypeptide expression has been detected in the testes, LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof may be useful in diagnosing or treating diseases and conditions affecting the testes. Examples of such diseases and conditions include, but are not limited to, male infertility and testicular carcinoma. Other diseases and conditions associated with the development and function of the testes are encompassed within the scope of this invention.

Since LGR8 polypeptide expression has been detected in the bone marrow, LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof may be useful in diagnosing or treating diseases and conditions affecting the bone marrow. Examples of such diseases and conditions include, but are not limited to, leukemia. Other diseases and conditions associated with the development and function of the bone marrow are encompassed within the scope of this invention.

Since LGR8 polypeptide expression has been detected in the fetal kidney, LGR8 nucleic acid molecules, polypeptides, and agonists and antagonists thereof may be useful in diagnosing or treating diseases and conditions affecting the kidney. Examples of such diseases and conditions include, but are not limited to, anemia, hypertension, and low blood pressure. Other diseases and conditions associated with the development and function of the kidney are encompassed within the scope of this invention.

Nucleic acid molecules of the invention (including those that do not themselves encode biologically active polypeptides) may be used to map the locations of the LGR8 gene and related genes on chromosomes. Mapping may be done by techniques known in the art, such as PCR amplification and *in situ* hybridization.

5 LGR8 nucleic acid molecules (including those that do not themselves encode biologically active polypeptides), may be useful as hybridization probes in diagnostic assays to test, either qualitatively or quantitatively, for the presence of an LGR8 nucleic acid molecule in mammalian tissue or bodily fluid samples.

Other methods may also be employed where it is desirable to inhibit the
10 activity of one or more LGR8 polypeptides. Such inhibition may be effected by nucleic acid molecules that are complementary to and hybridize to expression control sequences (triple helix formation) or to LGR8 mRNA. For example, antisense DNA or RNA molecules, which have a sequence that is complementary to at least a portion of an LGR8 gene can be introduced into the cell. Anti-sense probes may be designed
15 by available techniques using the sequence of the LGR8 gene disclosed herein. Typically, each such antisense molecule will be complementary to the start site (5' end) of each selected LGR8 gene. When the antisense molecule then hybridizes to the corresponding LGR8 mRNA, translation of this mRNA is prevented or reduced. Anti-sense inhibitors provide information relating to the decrease or absence of an
20 LGR8 polypeptide in a cell or organism.

Alternatively, gene therapy may be employed to create a dominant-negative inhibitor of one or more LGR8 polypeptides. In this situation, the DNA encoding a mutant polypeptide of each selected LGR8 polypeptide can be prepared and introduced into the cells of a patient using either viral or non-viral methods as
25 described herein. Each such mutant is typically designed to compete with endogenous polypeptide in its biological role.

In addition, an LGR8 polypeptide, whether biologically active or not, may be used as an immunogen, that is, the polypeptide contains at least one epitope to which antibodies may be raised. Selective binding agents that bind to an LGR8 polypeptide
30 (as described herein) may be used for *in vivo* and *in vitro* diagnostic purposes, including, but not limited to, use in labeled form to detect the presence of LGR8 polypeptide in a body fluid or cell sample. The antibodies may also be used to prevent, treat, or diagnose a number of diseases and disorders, including those recited herein. The antibodies may bind to an LGR8 polypeptide so as to diminish or block

encoding the mature form (*i.e.*, lacking the signal peptide) of human LGR8. These sequences were then used to design gene specific oligonucleotides for the identification of cDNA sources and the generation of cDNA clones, using various PCR strategies. Several highly homologous, but not identical, LGR8 sequences were thus isolated. An analysis of these sequences led to the identification of four nucleotide sequences encoding the mature forms (*i.e.*, the forms lacking an LGR8 start codon and the nucleotide sequence encoding the signal peptide) of LGR8-A, LGR8-B, LGR8-C, and LGR8-D.

The nucleotide sequence encoding the mature form of human LGR8-A was obtained in amplification reactions using 5 µl of a human adrenal Marathon Ready cDNA template (Clontech Laboratories; Palo Alto, CA), 1.0 µm each of the amplimers 5'-T-G-C-C-A-A-A-A-A-G-G-A-T-A-T-T-T-T-C-C-C-T-G-T-G-G-G-A-A-T-C-T-T-A-3' (SEQ ID NO: 27) and 5'-C-T-A-G-G-A-AA-C-T-G-G-T-T-T-C-A-T-T-A-T-A-C-T-G-T-C-T-C-C-A-A-G-T-G-T-T-A-T-T-T-T-G-T-T-C-A-3' (SEQ ID NO: 28), 200 µm of dNTPs, 2.5 U of *Pfu*Turbo DNA polymerase (Stratagene; La Jolla, CA), and 5 µL 10X *Pfu*Turbo DNA polymerase reaction buffer in a final volume of 50 µL. Reactions were performed at 94°C for 1 minute for one cycle; 94°C for 10 seconds, 60°C for 20 seconds, and 72°C for 5 minutes for 45 cycles; and 72°C for 7 minutes for one cycle.

The amplification mixture was separated on an agarose gel, the PCR products were isolated from the gel, and the products were then blunt-end cloned into pPCR-Script Amp SK(+) (Stratagene). A number of clones were sequenced, each containing highly homologous (but not identical) LGR8 nucleotide sequences. These sequences were used to compile the four nucleotide sequences encoding the mature forms (*i.e.*, the form lacking a start codon and a signal peptide) of LGR8-A, LGR8-B, LGR8-C, and LGR8-D.

To isolate cDNA sequences corresponding to the 5' end of the cDNA sequence for the immature form of human LGR8, 5' RACE was performed using 5 µL of a human adrenal Marathon Ready cDNA template, 1.0 µm each of the primers 5'-C-C-A-T-C-C-T-A-A-T-A-C-G-A-C-T-C-A-C-T-A-T-A-G-G-G-C-3' (SEQ ID NO: 29) and 5'-A-T-T-G-T-C-A-T-C-T-A-G-A-A-T-T-A-G-C-C-A-A-G-T-T-A-G-C-T-G-A-T-3' (SEQ ID NO: 30), 200 µm of dNTPs, 1 µL of 50X Advantage2 Polymerase Mix (Clontech Laboratories), and 5 µL 10X Advantage2 PCR buffer in a final volume of 50 µL. Reactions were performed at 94°C for 1 minute for one cycle;

cytoplasmic C-terminal region. Sequence analysis of the full-length LGR8-A coding sequence indicated that the cDNA comprises a 2262 bp open reading frame encoding a protein of 754 amino acids (Figures 1A-1D). The mature form of LGR8-A is 718 amino acids in length. LGR8-A is most closely related to glycoprotein hormone receptor LGR7 (Figures 10A-10B).

The LGR8-B coding sequence is identical to the LGR8-A coding sequence with the exception that the LGR8-B coding sequence lacks a portion of the sequence encoding the N-terminal extracellular domain. Sequence analysis of the full-length LGR8-B coding sequence indicated that the cDNA comprises a 2190 bp open reading frame encoding a protein of 730 amino acids (Figures 3A-3D). The mature form of LGR8-B is 694 amino acids in length.

The LGR8-C coding sequence is identical to the LGR8-A coding sequence with the exception that the LGR8-C coding sequence lacks a portion of sequence encoding the N-terminal extracellular domain. Sequence analysis of the full-length LGR8-C coding sequence indicated that the cDNA comprises a 2046 bp open reading frame encoding a protein of 682 amino acids (Figures 5A-5D). The mature form of LGR8-C is 646 amino acids in length.

The LGR8-D coding sequence consists of sequence encoding approximately 90% of the N-terminal extracellular domain of the LGR8-B coding sequence, but lacks sequence encoding the transmembrane domains and the cytoplasmic C-terminal region. Sequence analysis of the full-length LGR8-D coding sequence indicated that the cDNA comprises a 1098 bp open reading frame encoding a protein of 366 amino acids (Figures 7A-7B). The mature form of LGR8-D is 330 amino acids in length.

To identify cDNA sequences encoding murine LGR8-A, homology-based BLAST searches of a human genomic database were performed using the amino acid sequence of human LGR8-A. A number of sequences sharing a high degree of homology were found within a 213 kb mouse public genomic sequence (Accession No. AC077689). No exons, genes, or homologies to known genes were identified in the AC077689 sequence record. The sequences thus identified were curated by hand and electronically compiled to yield the complete nucleotide sequence encoding murine LGR8-A (Figures 8A-8D). A sequence comparison of the mature human and murine LGR8-A sequences indicates that the sequences share an 86.6% similarity and an 83.1% identity (Figures 11A-11B). A sequence comparison of the N-terminal extracellular domains (absent the signal peptide) of human and murine LGR8-A

an agarose gel, and PCR products of the expected size (319 bp) were identified in adult skeletal muscle, testis, and adrenal gland.

Intron-spanning PCR was next performed on proprietary oligo-dT primed and random primed human cDNA libraries for the following tissues: fetal stomach (oligo-dT primed), fetal stomach (random primed), pons/medulla (oligo-dT primed), breast tumor T1485 (oligo-dT primed), breast tumor T1485 (random primed), ovary tumor T22 (oligo-dT primed), ovary tumor T22 (random primed), fetal thymus (oligo-dT primed), fetal thymus (random primed), fetal mesentery (oligo-dT primed), fetal mesentery (random primed), placenta (oligo-dT primed), placenta (random primed),
10 Multiple cell lines [A204, A673, Hs729T, HISM and RD (oligo-dT primed)], Multiple cell lines [A204, A673, Hs729T, HISM and RD (random primed)], fetal pancreas (oligo-dT primed), fetal pancreas (random primed), lymphoma cell lines (oligo-dT primed), lymphoma cell lines (random primed), ovary tumor T23 (oligo-dT primed), ovary tumor T23 (random primed), colon tumor T25 (oligo-dT primed),
15 colon tumor T25 (random primed), adult T-cells (oligo-dT primed), normalized fetal tissue (random primed), fetal heart (oligo-dT primed), fetal heart (random primed), fetal bladder (oligo-dT primed), fetal bladder (random primed), fetal kidney (oligo-dT primed), fetal kidney (random primed), lung tumor T27 (oligo-dT primed), lung tumor T27 (random primed), fetal liver (oligo-dT primed), cytoplasmic breast carcinoma cell lines (oligo-dT primed), cytoplasmic breast carcinoma cell lines
20 (random primed), fetal spleen (oligo-dT primed), fetal spleen (random primed), uterus (oligo-dT primed), uterus (random primed), adrenal (oligo-dT primed), adrenal (random primed), forebrain (oligo-dT primed), forebrain (random primed), testis (oligo-dT primed), testis (random primed), colon tumor T24 (oligo-dT primed), colon
25 tumor T24 (random primed), fetal heart (oligo-dT primed), fetal scalp (oligo-dT primed), fetal scalp (random primed), fetal lung (oligo-dT primed), fetal lung (random primed), trachea (oligo-dT primed), trachea (random primed), cerebellum (oligo-dT primed), midbrain LNV block 10 (oligo-dT primed), midbrain LNV block 10 (random primed), prostate tumor T1940 (random primed), fetal ovary (oligo-dT
30 primed), fetal calveria (oligo-dT primed), fetal calveria (random primed), fetal gall bladder (oligo-dT primed), fetal gall bladder (random primed), spinal column (oligo-dT primed), spinal column (random primed), thalamus (oligo-dT primed), prostate tumor T1175 (oligo-dT primed), prostate tumor T1175 (random primed), breast tumor T1543 (oligo-dT primed), breast tumor T1543 (random primed), fetal skin (oligo-dT

performed as described above using 300 nm each of the primers 5'-G-T-C-G-A-C-G-G-C-G-A-G-C-C-C-3' (SEQ ID NO: 40) and 5'-T-C-T-T-T-G-G-G-A-C-C-T-T-G-T-C-T-G-C-A-A-3' (SEQ ID NO: 41) and 200 nm of the flurogenic probe 5'-(6-FAM)-T-G-G-G-C-C-G-C-G-T-C-T-C-C-T-T-T-G-A-G-C-T-(TAMRA)-3' (Primer Express, PE BioSystems, Foster City, CA; SEQ ID NO: 42; wherein "6-FAM" is the 5' reporter dye 6-carboxy-fluorescein and "TAMRA" is the 3' quencher 6-carboxytetramethylrhodamine). The highest levels of LGR8 mRNA expression were detected in skeletal muscle and uterus. Lower levels were found in adrenal and testis, with lower levels still in thalamus and bone marrow.

10

The expression of LGR8 mRNA is localized by *in situ* hybridization. A panel of normal embryonic and adult mouse tissues is fixed in 4% paraformaldehyde, embedded in paraffin, and sectioned at 5 μ m. Sectioned tissues are permeabilized in 0.2 M HCl, digested with Proteinase K, and acetylated with triethanolamine and acetic anhydride. Sections are prehybridized for 1 hour at 60°C in hybridization solution (300 mM NaCl, 20 mM Tris-HCl, pH 8.0, 5 mM EDTA, 1X Denhardt's solution, 0.2% SDS, 10 mM DTT, 0.25 mg/ml tRNA, 25 μ g/ml polyA, 25 μ g/ml polyC and 50% formamide) and then hybridized overnight at 60°C in the same solution containing 10% dextran and 2 x 10⁴ cpm/ μ l of a ³³P-labeled antisense riboprobe complementary to the human LGR8 gene. The riboprobe is obtained by *in vitro* transcription of a clone containing human LGR8 cDNA sequences using standard techniques.

20

Following hybridization, sections are rinsed in hybridization solution, treated with RNaseA to digest unhybridized probe, and then washed in 0.1X SSC at 55°C for 30 minutes. Sections are then immersed in NTB-2 emulsion (Kodak, Rochester, NY), exposed for 3 weeks at 4°C, developed, and counterstained with hematoxylin and eosin. Tissue morphology and hybridization signal are simultaneously analyzed by darkfield and standard illumination for brain (one sagittal and two coronal sections), gastrointestinal tract (esophagus, stomach, duodenum, jejunum, ileum, proximal colon, and distal colon), pituitary, liver, lung, heart, spleen, thymus, lymph nodes, kidney, adrenal, bladder, pancreas, salivary gland, male and female reproductive organs (ovary, oviduct, and uterus in the female; and testis, epididymus, prostate, seminal vesicle, and vas deferens in the male), BAT and WAT (subcutaneous, perirenal), bone (femur), skin, breast, and skeletal muscle.

30

B. Expression of LGR8 Polypeptide in Mammalian Cells

PCR is used to amplify template DNA sequences encoding an LGR8 polypeptide using primers corresponding to the 5' and 3' ends of the sequence. The amplified DNA products may be modified to contain restriction enzyme sites to allow
5 for insertion into expression vectors. PCR products are gel purified and inserted into expression vectors using standard recombinant DNA methodology. An exemplary expression vector, pCEP4 (Invitrogen, Carlsbad, CA), that contains an Epstein-Barr virus origin of replication, may be used for the expression of LGR8 polypeptides in 293-EBNA-1 cells. Amplified and gel purified PCR products are ligated into pCEP4
10 vector and introduced into 293-EBNA cells by lipofection. The transfected cells are selected in 100 µg/mL hygromycin and the resulting drug-resistant cultures are grown to confluence. The cells are then cultured in serum-free media for 72 hours. The conditioned media is removed and LGR8 polypeptide expression is analyzed by SDS-PAGE.

15 LGR8 polypeptide expression may be detected by silver staining. Alternatively, LGR8 polypeptide is produced as a fusion protein with an epitope tag, such as an IgG constant domain or a FLAG epitope, which may be detected by Western blot analysis using antibodies to the peptide tag.

LGR8 polypeptides may be excised from an SDS-polyacrylamide gel, or
20 LGR8 fusion proteins are purified by affinity chromatography to the epitope tag, and subjected to N-terminal amino acid sequence analysis as described herein.

C. Purification of LGR8 Polypeptide from Mammalian Cells

LGR8 polypeptide expression constructs are introduced into 293 EBNA or
25 CHO cells using either a lipofection or calcium phosphate protocol.

To conduct functional studies on the LGR8 polypeptides that are produced, large quantities of conditioned media are generated from a pool of hygromycin selected 293 EBNA clones. The cells are cultured in 500 cm Nunc Triple Flasks to 80% confluence before switching to serum-free media a week prior to harvesting the
30 media. Conditioned media is harvested and frozen at -20°C until the protein is to be purified.

Conditioned media is purified by affinity chromatography as described below. The media is thawed and then passed through a 0.2 µm filter. A Protein G column is equilibrated with PBS at pH 7.0, and then loaded with the filtered media. The column

changes that are informative as to the function of LGR8 polypeptide. Similarly, a construct containing the full-length LGR8 polypeptide under the control of the beta actin promoter is prepared. The delivery of this construct is expected to result in ubiquitous expression.

5 To generate these constructs, PCR is used to amplify template DNA sequences encoding an LGR8 polypeptide using primers that correspond to the 5' and 3' ends of the desired sequence and which incorporate restriction enzyme sites to permit insertion of the amplified product into an expression vector. Following amplification, PCR products are gel purified, digested with the appropriate restriction enzymes, and
10 ligated into an expression vector using standard recombinant DNA techniques. For example, amplified LGR8 polypeptide sequences can be cloned into an expression vector under the control of the human β -actin promoter as described by Graham *et al.*, 1997, *Nature Genetics*, 17:272-74 and Ray *et al.*, 1991, *Genes Dev.* 5:2265-73.

Following ligation, reaction mixtures are used to transform an *E. coli* host
15 strain by electroporation and transformants are selected for drug resistance. Plasmid DNA from selected colonies is isolated and subjected to DNA sequencing to confirm the presence of an appropriate insert and absence of mutation. The LGR8 polypeptide expression vector is purified through two rounds of CsCl density gradient centrifugation, cleaved with a suitable restriction enzyme, and the linearized fragment
20 containing the LGR8 polypeptide transgene is purified by gel electrophoresis. The purified fragment is resuspended in 5 mM Tris, pH 7.4, and 0.2 mM EDTA at a concentration of 2 mg/mL.

Single-cell embryos from BDF1 x BDF1 bred mice are injected as described (PCT Pub. No. WO 97/23614). Embryos are cultured overnight in a CO₂ incubator
25 and 15-20 two-cell embryos are transferred to the oviducts of a pseudopregnant CD1 female mice. Offspring obtained from the implantation of microinjected embryos are screened by PCR amplification of the integrated transgene in genomic DNA samples as follows. Ear pieces are digested in 20 mL ear buffer (20 mM Tris, pH 8.0, 10 mM EDTA, 0.5% SDS, and 500 mg/mL proteinase K) at 55°C overnight. The sample is
30 then diluted with 200 mL of TE, and 2 mL of the ear sample is used in a PCR reaction using appropriate primers.

At 8 weeks of age, transgenic founder animals and control animals are sacrificed for necropsy and pathological analysis. Portions of spleen are removed and total cellular RNA isolated from the spleens using the Total RNA Extraction Kit

chromagen (BioTek, Santa Barbara, CA). Sections are counterstained with hematoxylin.

After necropsy, MLN and sections of spleen and thymus from transgenic animals and control littermates are removed. Single cell suspensions are prepared by
5 gently grinding the tissues with the flat end of a syringe against the bottom of a 100 mm nylon cell strainer (Becton Dickinson, Franklin Lakes, NJ). Cells are washed twice, counted, and approximately 1×10^6 cells from each tissue are then incubated for 10 minutes with 0.5 μ g CD16/32(Fc γ III/II) Fc block in a 20 μ L volume. Samples
10 are then stained for 30 minutes at 2-8°C in a 100 μ L volume of PBS (lacking Ca^+ and Mg^+), 0.1% bovine serum albumin, and 0.01% sodium azide with 0.5 μ g antibody of FITC or PE-conjugated monoclonal antibodies against CD90.2 (Thy-1.2), CD45R (B220), CD11b(Mac-1), Gr-1, CD4, or CD8 (PharMingen, San Diego, CA). Following antibody binding, the cells are washed and then analyzed by flow cytometry on a FACScan (Becton Dickinson).

15

While the present invention has been described in terms of the preferred embodiments, it is understood that variations and modifications will occur to those skilled in the art. Therefore, it is intended that the appended claims cover all such equivalent variations that come within the scope of the invention as claimed.

has an activity of the encoded polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23, or is antigenic;

5 (d) a region of the nucleotide sequence of any of SEQ ID NO: 1, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 9, SEQ ID NO: 11, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 19, or SEQ ID NO: 22, or any of (a) - (c) comprising a fragment of at least about 16 nucleotides;

(e) a nucleotide sequence which hybridizes under moderately or highly
10 stringent conditions to the complement of any of (a) - (d); and

(f) a nucleotide sequence complementary to any of (a) - (d).

3. An isolated nucleic acid molecule comprising a nucleotide sequence selected from the group consisting of:

15 (a) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one conservative amino acid substitution, wherein the encoded polypeptide has an activity
20 of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(b) a nucleotide sequence encoding a polypeptide as set forth in any of
25 SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one amino acid insertion, wherein the encoded polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ
30 ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(c) a nucleotide sequence encoding a polypeptide as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ

5. A host cell comprising the vector of Claim 4.
6. The host cell of Claim 5 that is a eukaryotic cell.
- 5 7. The host cell of Claim 5 that is a prokaryotic cell.
8. A process of producing an LGR8 polypeptide comprising culturing the host cell of Claim 5 under suitable conditions to express the polypeptide, and
10 optionally isolating the polypeptide from the culture.
9. A polypeptide produced by the process of Claim 8.
10. The process of Claim 8, wherein the nucleic acid molecule comprises
15 promoter DNA other than the promoter DNA for the native LGR8 polypeptide operatively linked to the DNA encoding the LGR8 polypeptide.
11. The isolated nucleic acid molecule according to Claim 2, wherein the percent identity is determined using a computer program selected from the group
20 consisting of GAP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman algorithm.
12. A process for determining whether a compound inhibits LGR8 polypeptide activity or LGR8 polypeptide production comprising exposing a cell
25 according to any of Claims 5, 6, or 7 to the compound and measuring LGR8 polypeptide activity or LGR8 polypeptide production in said cell.
13. An isolated polypeptide comprising the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ
30 ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23.
14. An isolated polypeptide comprising the amino acid sequence selected from the group consisting of:

12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one conservative amino acid substitution, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(b) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one amino acid insertion, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(c) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one amino acid deletion, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23;

(d) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 which has a C- and/or N- terminal truncation, wherein the polypeptide has an activity of the polypeptide set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23; and

(e) the amino acid sequence as set forth in any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or SEQ ID NO: 23 with at least one modification selected from

22. The selective binding agent of Claim 18 that is a human antibody or fragment thereof.

23. The selective binding agent of Claim 18 that is a polyclonal antibody
5 or fragment thereof.

24. The selective binding agent Claim 18 that is a monoclonal antibody or fragment thereof.

10 25. The selective binding agent of Claim 18 that is a chimeric antibody or fragment thereof.

26. The selective binding agent of Claim 18 that is a CDR-grafted antibody or fragment thereof.

15 27. The selective binding agent of Claim 18 that is an antiidiotypic antibody or fragment thereof.

28. The selective binding agent of Claim 18 that is a variable region
20 fragment.

29. The variable region fragment of Claim 28 that is a Fab or a Fab' fragment.

25 30. A selective binding agent or fragment thereof comprising at least one complementarity determining region with specificity for a polypeptide having the amino acid sequence of any of SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 5, SEQ ID NO: 7, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 15, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 21, or
30 SEQ ID NO: 23.

31. The selective binding agent of Claim 18 that is bound to a detectable label.

41. The polypeptide of Claim 40 that is covalently modified with a water-soluble polymer.

42. The polypeptide of Claim 41, wherein the water-soluble polymer is
5 selected from the group consisting of polyethylene glycol, monomethoxy-polyethylene glycol, dextran, cellulose, poly-(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide copolymers, polyoxyethylated polyols, and polyvinyl alcohol.

10 43. A composition comprising a nucleic acid molecule of any of Claims 1, 2, or 3 and a pharmaceutically acceptable formulation agent.

44. The composition of Claim 43, wherein said nucleic acid molecule is contained in a viral vector.

15

45. A viral vector comprising a nucleic acid molecule of any of Claims 1, 2, or 3.

46. A fusion polypeptide comprising the polypeptide of any of Claims 13,
20 14, or 15 fused to a heterologous amino acid sequence.

47. The fusion polypeptide of Claim 46, wherein the heterologous amino acid sequence is an IgG constant domain or fragment thereof.

25 48. A method for treating, preventing, or ameliorating a medical condition comprising administering to a patient the polypeptide of any of Claims 13, 14, or 15, or the polypeptide encoded by the nucleic acid of any of Claims 1, 2, or 3.

49. A method of diagnosing a pathological condition or a susceptibility to
30 a pathological condition in a subject comprising:

(a) determining the presence or amount of expression of the polypeptide of any of Claims 13, 14, or 15, or the polypeptide encoded by the nucleic acid molecule of any of Claims 1, 2, or 3 in a sample; and

56. A nucleic acid molecule of any of Claims 1, 2, or 3 attached to a solid support.

57. An array of nucleic acid molecules comprising at least one nucleic acid molecule of any of Claims 1, 2, or 3.

58. An isolated polypeptide comprising the amino acid sequence as set forth in SEQ ID NO: 2 with at least one conservative amino acid substitution selected from the group consisting of: isoleucine at position 26; valine at position 41; isoleucine at position 55; aspartic acid at position 78; aspartic acid at position 123; arginine at position 130; valine at position 135; methionine at position 142; leucine at position 166; tyrosine at position 167; lysine at position 201; valine at position 204; isoleucine at position 216; glutamic acid at position 217; leucine at position 221; leucine at position 240; leucine at position 252; isoleucine at position 277; methionine at position 288; lysine at position 290; isoleucine at position 324; isoleucine at position 341; isoleucine at position 344; aspartic acid at position 350; leucine at position 376; valine at position 420; valine at position 425; valine at position 427; isoleucine at position 434; tyrosine at position 442; arginine at position 444; tyrosine at position 450; isoleucine at position 466; isoleucine at position 471; leucine at position 476; phenylalanine at position 478; glutamic acid at position 481; histidine at position 485; phenylalanine at position 515; tyrosine at position 521; isoleucine at position 522; tyrosine at position 526; valine at position 531; valine at position 541; isoleucine at position 551; valine at position 552; glutamic acid at position 561; phenylalanine at position 562; tyrosine at position 566; tyrosine at position 577; aspartic acid at position 579; isoleucine at position 597; isoleucine at position 603; valine at position 616; isoleucine at position 621; isoleucine at position 626; lysine at position 632; leucine at position 649; isoleucine at position 654; valine at position 675; isoleucine at position 682; glutamic acid at position 700; isoleucine at position 702; tyrosine at position 707; tyrosine at position 709; isoleucine at position 727; valine at position 729; methionine at position 737; methionine at position 745; and leucine at position 749; wherein the polypeptide has an activity of the polypeptide as set forth in SEQ ID NO: 2.

FIG. 1A

atg att gtt ttt ctg gtt ttt aaa cat ctc ttc agc ctc aga ttg att	48
Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile	
1 5 10 15	
aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat	96
Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp	
20 25 30	
ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga	144
Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly	
35 40 45	
tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac	192
Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His	
50 55 60	
tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt	240
Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys	
65 70 75 80	
ggg gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta tat ctc	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu	
180 185 190	
aac cac aac tgc atc aca acc ctc aga cct gga ata ttc aaa gac tta	624
Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu	
195 200 205	

FIG. 1B

cat cag cta act tgg cta att cta gat gac aat cca ata acc aga att	672
His Gln Leu Thr Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile	
210 215 220	
tca cag cgc ttg ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg	720
Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met	
225 230 235 240	
gtt aat aac tac tta gaa gct ctt ccc aag cag atg tgt gcc caa atg	768
Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met	
245 250 255	
cct caa ctc aac tgg gtg gat ttg gaa ggc aat aga ata aag tat ctc	816
Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu	
260 265 270	
aca aat tct acg ttt ctg tcg tgc gat tcg ctc aca gtg ctg ttt ctg	864
Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Phe Leu	
275 280 285	
cct aga aat caa att ggt ttt gtt cca gag aag aca ttt tct tca tta	912
Pro Arg Asn Gln Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu	
290 295 300	
aaa aat tta gga gaa ctg gat ctg tct agc aat acg ata acg gag cta	960
Lys Asn Leu Gly Glu Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu	
305 310 315 320	
tca cct cac ctt ttt aaa gac ttg aag ctt cta caa aag ctg aac ctg	1008
Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asn Leu	
325 330 335	
tca tcc aat cct ctt atg tat ctt cac aag aac cag ttt gaa agt ctt	1056
Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln Phe Glu Ser Leu	
340 345 350	
aaa caa ctt cag tct cta gac ctg gaa agg ata gag att cca aat ata	1104
Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile	
355 360 365	
aac aca cga atg ttt caa ccc atg aag aat ctt tct cac att tat ttc	1152
Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Phe	
370 375 380	
aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc cga ata tgt atg	1200
Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met	
385 390 395 400	
ccc ttg acg gac ggc att tct tca ttt gag gac ctc ttg gct aac aat	1248
Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn Asn	
405 410 415	

FIG. 1C

atc ctc aga ata ttt gtc tgg gtt ata gct ttc att acc tgc ttt gga	1296
Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe Gly	
420 425 430	
aat ctt ttt gtc att ggc atg aga tct ttc att aaa gct gaa aat aca	1344
Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn Thr	
435 440 445	
act cac gct atg tcc atc aaa atc ctt tgt tgt gct gat tgc ctg atg	1392
Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met	
450 455 460	
ggt gtt tac ttg ttc ttt gtt ggc att ttc gat ata aaa tac cga ggg	1440
Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg Gly	
465 470 475 480	
cag tat cag aag tat gcc ttg ctg tgg atg gag agc gtg cag tgc cgc	1488
Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys Arg	
485 490 495	
ctc atg ggg ttc ctg gcc atg ctg tcc acc gaa gtc tct gtt ctg cta	1536
Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu Leu	
500 505 510	
ctg acc tac ttg act ttg gag aag ttc ctg gtc att gtc ttc ccc ttc	1584
Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe	
515 520 525	
agt aac att cga cct gga aaa cgg cag acc tca gtc atc ctc att tgc	1632
Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile Cys	
530 535 540	
atc tgg atg gcg gga ttt tta ata gct gta att cca ttt tgg aat aag	1680
Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn Lys	
545 550 555 560	
gat tat ttt gga aac ttt tat ggg aaa aat gga gta tgt ttc cca ctt	1728
Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu	
565 570 575	
tat tat gac caa aca gaa gat att gga agc aaa ggg tat tct ctt gga	1776
Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu Gly	
580 585 590	
att ttc cta ggt gtg aac ttg ctg gct ttt ctc atc att gtg ttt tcc	1824
Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe Ser	
595 600 605	
tat att act atg ttc tgt tcc att caa aaa acc gcc ttg cag acc aca	1872
Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr Thr	
610 615 620	

FIG. 2A

caa ggt agc atg atc act cct tca tgc caa aaa gga tat ttt ccc tgt	48
Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys	
1 5 10 15	
ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys	
20 25 30	
gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg	192
Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val	
50 55 60	
gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac	240
Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp	
65 70 75 80	
tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg	288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val	
85 90 95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa	336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa	384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys	
115 120 125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca	432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala	
130 135 140	
ttt ttt gga tta tgt aat ctg caa ata tta tat ctc aac cac aac tgc	480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys	
145 150 155 160	
atc aca acc ctc aga cct gga ata ttc aaa gac tta cat cag cta act	528
Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr	
165 170 175	
tgg cta att cta gat gac aat cca ata acc aga att tca cag cgc ttg	576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu	
180 185 190	
ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac	624
Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr	
195 200 205	

FIG. 2B

tta gaa gct ctt ccc aag cag atg tgt gcc caa atg cct caa ctc aac	672
Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn	
210 215 220	
tggtgtgat ttg gaa ggc aat aga ata aag tat ctc aca aat tct acg	720
Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr	
225 230 235 240	
ttt ctg tct tgc gat tct ctc aca gtg ctg ttt ctg cct aga aat caa	768
Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln	
245 250 255	
att ggt ttt gtt cca gag aag aca ttt tct tca tta aaa aat tta gga	816
Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly	
260 265 270	
gaa ctg gat ctg tct agc aat acg ata acg gag cta tca cct cac ctt	864
Glu Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu	
275 280 285	
ttt aaa gac ttg aag ctt cta caa aag ctg aac ctg tca tcc aat cct	912
Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro	
290 295 300	
ctt atg tat ctt cac aag aac cag ttt gaa agt ctt aaa caa ctt cag	960
Leu Met Tyr Leu His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln	
305 310 315 320	
tct cta gac ctg gaa agg ata gag att cca aat ata aac aca cga atg	1008
Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met	
325 330 335	
ttt caa ccc atg aag aat ctt tct cac att tat ttc aaa aac ttt cga	1056
Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg	
340 345 350	
tac tgc tcc tat gct ccc cat gtc cga ata tgt atg ccc ttg acg gac	1104
Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp	
355 360 365	
ggc att tct tca ttt gag gac ctc ttg gct aac aat atc ctc aga	1149
Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg	
370 375 380	

FIG. 3A

atg att gtt ttt ctg gtt ttt aaa cat ctc ttc agc ctc aga ttg att	48
Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile	
1 5 10 15	
aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat	96
Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp	
20 25 30	
ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga	144
Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly	
35 40 45	
tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac	192
Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His	
50 55 60	
tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt	240
Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys	
65 70 75 80	
ggg gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta tat ctc	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu	
180 185 190	
aac cac aac tgc atc aca acc ctc aga cct gga ata ttc aaa gac tta	624
Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu	
195 200 205	

FIG. 3B

cat	cag	cta	act	tgg	cta	att	cta	gat	gac	aat	cca	ata	acc	aga	att	672
His	Gln	Leu	Thr	Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile	
210						215				220						
tca	cag	cgc	ttg	ttt	acg	gga	tta	aat	tcc	ttg	ttt	ttc	ctg	tct	atg	720
Ser	Gln	Arg	Leu	Phe	Thr	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met	
225					230				235						240	
gtt	aat	aac	tac	tta	gaa	gct	ctt	ccc	aag	cag	atg	tgt	gcc	caa	atg	768
Val	Asn	Asn	Tyr		Leu	Glu	Ala	Leu	Pro	Lys	Gln	Met	Cys	Ala	Gln	Met
				245					250					255		
cct	caa	ctc	aac	tgg	gtg	gat	ttg	gaa	ggc	aat	aga	ata	aag	tat	ctc	816
Pro	Gln	Leu	Asn	Trp	Val	Asp	Leu	Glu	Gly	Asn	Arg	Ile	Lys	Tyr	Leu	
			260					265					270			
aca	aat	tct	acg	ttt	ctg	tcg	tgc	gat	tgc	ctc	aca	gtg	ctg	gat	ctg	864
Thr	Asn	Ser	Thr	Phe	Leu	Ser	Cys	Asp	Ser	Leu	Thr	Val	Leu	Asp	Leu	
	275						280					285				
tct	agc	aat	acg	ata	acg	gag	cta	tca	cct	cac	ctt	ttt	aaa	gac	ttg	912
Ser	Ser	Asn	Thr	Ile	Thr	Glu	Leu	Ser	Pro	His	Leu	Phe	Lys	Asp	Leu	
	290					295					300					
aag	ctt	cta	caa	aag	ctg	aac	ctg	tca	tcc	aat	cct	ctt	atg	tat	ctt	960
Lys	Leu	Leu	Gln	Lys	Leu	Asn	Leu	Ser	Ser	Asn	Pro	Leu	Met	Tyr	Leu	
305					310					315					320	
cac	aag	aac	cag	ttt	gaa	agt	ctt	aaa	caa	ctt	cag	tct	cta	gac	ctg	1008
His	Lys	Asn	Gln	Phe	Glu	Ser	Leu	Lys	Gln	Leu	Gln	Ser	Leu	Asp	Leu	
			325					330						335		
gaa	agg	ata	gag	att	cca	aat	ata	aac	aca	cga	atg	ttt	caa	ccc	atg	1056
Glu	Arg	Ile	Glu	Ile	Pro	Asn	Ile	Asn	Thr	Arg	Met	Phe	Gln	Pro	Met	
			340					345					350			
aag	aat	ctt	tct	cac	att	tat	ttc	aaa	aac	ttt	cga	tac	tgc	tcc	tat	1104
Lys	Asn	Leu	Ser	His	Ile	Tyr	Phe	Lys	Asn	Phe	Arg	Tyr	Cys	Ser	Tyr	
		355					360					365				
gct	ccc	cat	gtc	cga	ata	tgt	atg	ccc	ttg	acg	gac	ggc	att	tct	tca	1152
Ala	Pro	His	Val	Arg	Ile	Cys	Met	Pro	Leu	Thr	Asp	Gly	Ile	Ser	Ser	
	370					375					380					
ttt	gag	gac	ctc	ttg	gct	aac	aat	atc	ctc	aga	ata	ttt	gtc	tgg	gtt	1200
Phe	Glu	Asp	Leu	Leu	Ala	Asn	Asn	Ile	Leu	Arg	Ile	Phe	Val	Trp	Val	
385					390					395					400	
ata	gct	ttc	att	acc	tgc	ttt	gga	aat	ctt	ttt	gtc	att	ggc	atg	aga	1248
Ile	Ala	Phe	Ile	Thr	Cys	Phe	Gly	Asn	Leu	Phe	Val	Ile	Gly	Met	Arg	
			405					410						415		

FIG. 3C

tct ttc att aaa gct gaa aat aca act cac gct atg tcc atc aaa atc	1296
Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile	
420 425 430	
ctt tgt tgt gct gat tgc ctg atg ggt gtt tac ttg ttc ttt gtt ggc	1344
Leu Cys Cys Ala Asp Cys Leu Met Gly Val Tyr Leu Phe Phe Val Gly	
435 440 445	
att ttc gat ata aaa tac cga ggg cag tat cag aag tat gcc ttg ctg	1392
Ile Phe Asp Ile Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu	
450 455 460	
tgg atg gag agc gtg cag tgc cgc ctc atg ggg ttc ctg gcc atg ctg	1440
Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu	
465 470 475 480	
tcc acc gaa gtc tct gtt ctg cta ctg acc tac ttg act ttg gag aag	1488
Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu Glu Lys	
485 490 495	
ttc ctg gtc att gtc ttc ccc ttc agt aac att cga cct gga aaa cgg	1536
Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg Pro Gly Lys Arg	
500 505 510	
cag acc tca gtc atc ctc att tgc atc tgg atg gcg gga ttt tta ata	1584
Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala Gly Phe Leu Ile	
515 520 525	
gct gta att cca ttt tgg aat aag gat tat ttt gga aac ttt tat ggg	1632
Ala Val Ile Pro Phe Trp Asn Lys Asp Tyr Phe Gly Asn Phe Tyr Gly	
530 535 540	
aaa aat gga gta tgt ttc cca ctt tat tat gac caa aca gaa gat att	1680
Lys Asn Gly Val Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu Asp Ile	
545 550 555 560	
gga agc aaa ggg tat tct ctt gga att ttc cta ggt gtg aac ttg ctg	1728
Gly Ser Lys Gly Tyr Ser Leu Gly Ile Phe Leu Gly Val Asn Leu Leu	
565 570 575	
gct ttt ctc atc att gtg ttt tcc tat att act atg ttc tgt tcc att	1776
Ala Phe Leu Ile Ile Val Phe Ser Tyr Ile Thr Met Phe Cys Ser Ile	
580 585 590	
caa aaa acc gcc ttg cag acc aca gaa gta agg aat tgt ttt gga aga	1824
Gln Lys Thr Ala Leu Gln Thr Thr Glu Val Arg Asn Cys Phe Gly Arg	
595 600 605	
gag gtg gct gtt gca aat cgt ttc ttt ttt ata gtg ttc tct gat gcc	1872
Glu Val Ala Val Ala Asn Arg Phe Phe Phe Ile Val Phe Ser Asp Ala	
610 615 620	

FIG. 4A

caa ggt agc atg atc act cct tca tgc caa aaa gga tat ttt ccc tgt	48
Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys	
1 5 10 15	
ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys	
20 25 30	
gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg	192
Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val	
50 55 60	
gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac	240
Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp	
65 70 75 80	
tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg	288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val	
85 90 95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa	336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa	384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys	
115 120 125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca	432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala	
130 135 140	
ttt ttt gga tta tgt aat ctg caa ata tta tat ctc aac cac aac tgc	480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys	
145 150 155 160	
atc aca acc ctc aga cct gga ata ttc aaa gac tta cat cag cta act	528
Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr	
165 170 175	
tgg cta att cta gat gac aat cca ata acc aga att tca cag cgc ttg	576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu	
180 185 190	
ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac	624
Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr	
195 200 205	

FIG. 4B

tta gaa gct ctt ccc aag cag atg tgt gcc caa atg cct caa ctc aac	672
Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn	
210 215 220	
ttg gtg gat ttg gaa ggc aat aga ata aag tat ctc aca aat tct acg	720
Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr	
225 230 235 240	
ttt ctg tcg tgc gat tcg ctc aca gtg ctg gat ctg tct agc aat acg	768
Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr	
245 250 255	
ata acg gag cta tca cct cac ctt ttt aaa gac ttg aag ctt cta caa	816
Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln	
260 265 270	
aag ctg aac ctg tca tcc aat cct ctt atg tat ctt cac aag aac cag	864
Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln	
275 280 285	
ttt gaa agt ctt aaa caa ctt cag tct cta gac ctg gaa agg ata gag	912
Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu	
290 295 300	
att cca aat ata aac aca cga atg ttt caa ccc atg aag aat ctt tct	960
Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser	
305 310 315 320	
cac att tat ttc aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc	1008
His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val	
325 330 335	
cga ata tgt atg ccc ttg acg gac ggc att tct tca ttt gag gac ctc	1056
Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu	
340 345 350	
ttg gct aac aat atc ctc aga	1077
Leu Ala Asn Asn Ile Leu Arg	
355	

FIG. 5A

atg att gtt ttt ctg gtt ttt aaa cat ctc ttc agc ctc aga ttg att	48
Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile	
1 5 10 15	
aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat	96
Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp	
20 25 30	
ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga	144
Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly	
35 40 45	
tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac	192
Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His	
50 55 60	
tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt	240
Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys	
65 70 75 80	
ggt gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta att cta	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu	
180 185 190	
gat gac aat cca ata acc aga att tca cag cgc ttg ttt acg gga tta	624
Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu	
195 200 205	

FIG. 5B

aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac tta gaa gct ctt	672
Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu	
210 215 220	
ccc aag cag atg tgt gcc caa atg cct caa ctc aac tgg gtg gat ttg	720
Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu	
225 230 235 240	
gaa ggc aat aga ata aag tat ctc aca aat tct acg ttt ctg tcg tgc	768
Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys	
245 250 255	
gat tcg ctc aca gtg ctg gat ctg tct agc aat acg ata acg gag cta	816
Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu	
260 265 270	
tca cct cac ctt ttt aaa gac ttg aag ctt cta caa aag cta gac ctg	864
Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu	
275 280 285	
gaa agg ata gag att cca aat ata aac aca cga atg ttt caa ccc atg	912
Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met	
290 295 300	
aag aat ctt tct cac att tat ttc aaa aac ttt cga tac tgc tcc tat	960
Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr	
305 310 315 320	
gct ccc cat gtc cga ata tgt atg ccc ttg acg gac ggc att tct tca	1008
Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser	
325 330 335	
ttt gag gac ctc ttg gct aac aat atc ctc aga ata ttt gtc tgg gtt	1056
Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val	
340 345 350	
ata gct ttc att acc tgc ttt gga aat ctt ttt gtc att ggc atg aga	1104
Ile Ala Phe Ile Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg	
355 360 365	
tct ttc att aaa gct gaa aat aca act cac gct atg tcc atc aaa atc	1152
Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile	
370 375 380	
ctt tgt tgt gct gat tgc ctg atg ggt gtt tac ttg ttc ttt gtt ggc	1200
Leu Cys Cys Ala Asp Cys Leu Met Gly Val Tyr Leu Phe Phe Val Gly	
385 390 395 400	
att ttc gat ata aaa tac cga ggg cag tat cag aag tat gcc ttg ctg	1248
Ile Phe Asp Ile Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu	
405 410 415	

FIG. 5C

tgg atg gag agc gtg cag tgc cgc ctc atg ggg ttc ctg gcc atg ctg	1296
Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu	
420 425 430	
tcc acc gaa gtc tct gtt ctg cta ctg acc tac ttg act ttg gag aag	1344
Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu Glu Lys	
435 440 445	
ttc ctg gtc att gtc ttc ccc ttc agt aac att cga cct gga aaa cgg	1392
Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg Pro Gly Lys Arg	
450 455 460	
cag acc tca gtc atc ctc att tgc atc tgg atg gcg gga ttt tta ata	1440
Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala Gly Phe Leu Ile	
465 470 475 480	
gct gta att cca ttt tgg aat aag gat tat ttt gga aac ttt tat ggg	1488
Ala Val Ile Pro Phe Trp Asn Lys Asp Tyr Phe Gly Asn Phe Tyr Gly	
485 490 495	
aaa aat gga gta tgt ttc cca ctt tat tat gac caa aca gaa gat att	1536
Lys Asn Gly Val Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu Asp Ile	
500 505 510	
gga agc aaa ggg tat tct ctt gga att ttc cta ggt gtg aac ttg ctg	1584
Gly Ser Lys Gly Tyr Ser Leu Gly Ile Phe Leu Gly Val Asn Leu Leu	
515 520 525	
gct ttt ctc atc att gtg ttt tcc tat att act atg ttc tgt tcc att	1632
Ala Phe Leu Ile Ile Val Phe Ser Tyr Ile Thr Met Phe Cys Ser Ile	
530 535 540	
caa aaa acc gcc ttg cag acc aca gaa gta agg aat tgt ttt gga aga	1680
Gln Lys Thr Ala Leu Gln Thr Thr Glu Val Arg Asn Cys Phe Gly Arg	
545 550 555 560	
gag gtg gct gtt gca aat cgt ttc ttt ttt ata gtg ttc tct gat gcc	1728
Glu Val Ala Val Ala Asn Arg Phe Phe Phe Ile Val Phe Ser Asp Ala	
565 570 575	
atc tgc tgg att cct gta ttt gta gtt aaa atc ctt tcc ctc ttc cgg	1776
Ile Cys Trp Ile Pro Val Phe Val Val Lys Ile Leu Ser Leu Phe Arg	
580 585 590	
gtg gaa ata cca gac aca atg act tcc tgg ata gtg att ttt ttc ctt	1824
Val Glu Ile Pro Asp Thr Met Thr Ser Trp Ile Val Ile Phe Phe Leu	
595 600 605	
cca gtt aac agt gct ttg aat cca atc ctc tat act ctc aca acc aac	1872
Pro Val Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Asn	
610 615 620	

FIG. 6A

caa ggt agc atg atc act cct tca tgc caa aaa gga tat ttt ccc tgt	48
Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys	
1 5 10 15	
ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys	
20 25 30	
gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg	192
Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val	
50 55 60	
gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac	240
Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp	
65 70 75 80	
tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg	288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val	
85 90 95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa	336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa	384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys	
115 120 125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca	432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala	
130 135 140	
ttt ttt gga tta tgt aat ctg caa ata tta att cta gat gac aat cca	480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu Asp Asp Asn Pro	
145 150 155 160	
ata acc aga att tca cag cgc ttg ttt acg gga tta aat tcc ttg ttt	528
Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe	
165 170 175	
ttc ctg tct atg gtt aat aac tac tta gaa gct ctt ccc aag cag atg	576
Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met	
180 185 190	
tgt gcc caa atg cct caa ctc aac tgg gtg gat ttg gaa ggc aat aga	624
Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg	
195 200 205	

FIG. 6B

ata aag tat ctc aca aat tct acg ttt ctg tgc gat tgc ctc aca	672
Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr	
210 215 220	
gtg ctg gat ctg tct agc aat acg ata acg gag cta tca cct cac ctt	720
Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu	
225 230 235 240	
ttt aaa gac ttg aag ctt cta caa aag cta gac ctg gaa agg ata gag	768
Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu Glu Arg Ile Glu	
245 250 255	
att cca aat ata aac aca cga atg ttt caa ccc atg aag aat ctt tct	816
Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser	
260 265 270	
cac att tat ttc aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc	864
His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val	
275 280 285	
cga ata tgt atg ccc ttg acg gac ggc att tct tca ttt gag gac ctc	912
Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu	
290 295 300	
ttg gct aac aat atc ctc aga	933
Leu Ala Asn Asn Ile Leu Arg	
305 310	

FIG. 7A

atg att gtt ttt ctg gtt ttt aaa cat ctc ttc agc ctc aga ttg att	48
Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile	
1 5 10 15	
aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat	96
Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp	
20 25 30	
ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga	144
Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly	
35 40 45	
tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac	192
Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His	
50 55 60	
tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt	240
Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys	
65 70 75 80	
ggg gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta tat ctc	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu	
180 185 190	
aac cac aac tgc atc aca acc ctc aga cct gga ata ttc aaa gac tta	624
Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu	
195 200 205	

FIG. 7B

cat cag cta act tgg cta att cta gat gac aat cca ata acc aga att	672
His Gln Leu Thr Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile	
210 215 220	
tca cag cgc ttg ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg	720
Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met	
225 230 235 240	
gtt aat aac tac tta gaa gct ctt ccc aag cag atg tgt gcc caa atg	768
Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met	
245 250 255	
cct caa ctc aac tgg gtg gat ttg gaa ggc aat aga ata aag tat ctc	816
Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu	
260 265 270	
aca aat tct acg ttt ctg tgc tgc gat tgc ctc aca gtg ctg gat ctg	864
Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu	
275 280 285	
tct agc aat acg ata acg gag cta tca cct cac ctt ttt aaa gac ttg	912
Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu	
290 295 300	
aag ctt cta caa aag ctg aac ctg tca tcc aat cct ctt atg tat ctt	960
Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu	
305 310 315 320	
cac aag aac cag ttt gaa agt ctt aaa caa ctt cag tct cta gac ctg	1008
His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu	
325 330 335	
gaa agg ata gag att cca aat ata aac aca cga atg ttt caa ccc atg	1056
Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met	
340 345 350	
aag aat ctt tct cac ata gtt caa tat tat gat gtg ccg aca tga	1101
Lys Asn Leu Ser His Ile Val Gln Tyr Tyr Asp Val Pro Thr	
355 360 365	

FIG. 8A

atg	tgg	ctc	cta	ctt	cat	gtc	atc	ctt	ctg	aca	gag	gtc	aaa	gat	ttt	48
Met	Trp	Leu	Leu	Leu	His	Val	Ile	Leu	Leu	Thr	Glu	Val	Lys	Asp	Phe	
1				5					10					15		
gca	ctg	gct	gac	agc	agt	atg	gtg	gct	cct	ctg	tgc	ccc	aaa	ggg	tat	96
Ala	Leu	Ala	Asp	Ser	Ser	Met	Val	Ala	Pro	Leu	Cys	Pro	Lys	Gly	Tyr	
			20					25					30			
ttt	ccc	tgt	ggg	aat	ctc	acc	aaa	tgc	ttg	ccc	cga	gcc	ttt	cac	tgc	144
Phe	Pro	Cys	Gly	Asn	Leu	Thr	Lys	Cys	Leu	Pro	Arg	Ala	Phe	His	Cys	
		35					40					45				
gat	ggg	gtg	gat	gat	tgc	ggg	aat	ggg	gcc	gac	gag	gac	aac	tgt	ggg	192
Asp	Gly	Val	Asp	Asp	Cys	Gly	Asn	Gly	Ala	Asp	Glu	Asp	Asn	Cys	Gly	
	50					55					60					
gac	act	agt	gga	tgg	aca	acc	ata	ttt	ggc	aca	gtc	cat	ggg	aat	gtc	240
Asp	Thr	Ser	Gly	Trp	Thr	Thr	Ile	Phe	Gly	Thr	Val	His	Gly	Asn	Val	
65					70					75					80	
aat	aaa	gtg	aca	ttg	aca	cag	gag	tgc	ttt	ctc	agc	cag	tat	cca	cag	288
Asn	Lys	Val	Thr	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Ser	Gln	Tyr	Pro	Gln	
				85					90					95		
cac	tgt	tac	tgc	aga	gaa	aat	gaa	ctg	gaa	tgt	gta	aag	gct	gac	tta	336
His	Cys	Tyr	Cys	Arg	Glu	Asn	Glu	Leu	Glu	Cys	Val	Lys	Ala	Asp	Leu	
			100					105					110			
aaa	gct	gtg	cca	aag	gtt	tcc	agc	aac	gta	aca	tta	cta	tct	ctt	aag	384
Lys	Ala	Val	Pro	Lys	Val	Ser	Ser	Asn	Val	Thr	Leu	Leu	Ser	Leu	Lys	
		115					120					125				
aaa	aac	aaa	atc	cac	aga	ctt	cca	gtc	aag	gtc	ttc	agc	aga	tac	aca	432
Lys	Asn	Lys	Ile	His	Arg	Leu	Pro	Val	Lys	Val	Phe	Ser	Arg	Tyr	Thr	
	130					135					140					
gaa	ctc	aga	aag	ata	tac	ctt	cag	cac	aac	tgc	atc	aca	cac	atc	tcc	480
Glu	Leu	Arg	Lys	Ile	Tyr	Leu	Gln	His	Asn	Cys	Ile	Thr	His	Ile	Ser	
145				150						155					160	
agg	aga	gca	ttc	ctt	gga	tta	cat	aat	cta	caa	ata	ctg	tat	ctc	agc	528
Arg	Arg	Ala	Phe	Leu	Gly	Leu	His	Asn	Leu	Gln	Ile	Leu	Tyr	Leu	Ser	
				165					170					175		
cat	aac	tgc	att	acc	tct	ctc	agg	cct	ggg	ata	ttc	aaa	gac	ttg	cat	576
His	Asn	Cys	Ile	Thr	Ser	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu	His	
			180					185					190			
cag	ctt	gct	tgg	cta	att	tta	gat	gac	aac	cag	atc	acc	aga	atc	tca	624
Gln	Leu	Ala	Trp	Leu	Ile	Leu	Asp	Asn	Pro	Ile	Thr	Arg	Ile	Ser		
		195					200					205				

FIG. 8B

cag aag tcc ttt atg ggg tta aac tcc ttg ttt ttc ttg tcc atg gtg	672
Gln Lys Ser Phe Met Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val	
210 215 220	
ggt aac cgg ctc gag gcc ctt cct gaa aca ttg tgt gct cag atg cct	720
Gly Asn Arg Leu Glu Ala Leu Pro Glu Thr Leu Cys Ala Gln Met Pro	
225 230 235 240	
caa ctc aac tgg gtg gat ctg gca aac aat gga ata aag tac ata acg	768
Gln Leu Asn Trp Val Asp Leu Ala Asn Asn Gly Ile Lys Tyr Ile Thr	
245 250 255	
aac tcc acc ttc cta acg tgc gac tcg ctc acg gtt ctg ttt ctg cct	816
Asn Ser Thr Phe Leu Thr Cys Asp Ser Leu Thr Val Leu Phe Leu Pro	
260 265 270	
aga aat caa att ggt ttt gtt cca gag aag aca ttt tct tca tta aaa	864
Arg Asn Gln Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys	
275 280 285	
aat tta gga gaa ctg gac ctg tct agc aat atg ata aca aaa ctc cca	912
Asn Leu Gly Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro	
290 295 300	
gtc cac ctt ttc agc gac ctt cat ctt ctc cag aag ctg aac ctg tca	960
Val His Leu Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser	
305 310 315 320	
tcc aac cct ctt ctg tat gtc cac aag aac cag ttt gga agt ctc aaa	1008
Ser Asn Pro Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys	
325 330 335	
caa ctt cag tct cta gac ctg gaa agg ata gag att cca aac ata agc	1056
Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Ser	
340 345 350	
aca gga atg ttc cag cca atg aag aac ctt tct cac att tat ttg aaa	1104
Thr Gly Met Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Leu Lys	
355 360 365	
acc ttt cga tac tgc tcc tat gtc ccc cat gtc cga atc tgt atg ccg	1152
Thr Phe Arg Tyr Cys Ser Tyr Val Pro His Val Arg Ile Cys Met Pro	
370 375 380	
tcg act gat ggt att tct tcg tct gag gac ctc ttg gct aac ggt atc	1200
Ser Thr Asp Gly Ile Ser Ser Ser Glu Asp Leu Leu Ala Asn Gly Ile	
385 390 395 400	
ctc aga gtg tct gtc tgg gtt ata gct ttc att acc tgc gtt ggg aat	1248
Leu Arg Val Ser Val Trp Val Ile Ala Phe Ile Thr Cys Val Gly Asn	
405 410 415	

FIG. 8C

ttc ctt gtc ata gcc gtg aga tct ctc att aag gct gag aat aca act	1296
Phe Leu Val Ile Ala Val Arg Ser Leu Ile Lys Ala Glu Asn Thr Thr	
420 425 430	
cac gct atg tcc atc aaa atc ctt tgt tgt gcc gat tgc ctg atg ggg	1344
His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met Gly	
435 440 445	
gtg tac ctg ttc tcc gtg ggc gtc ttt gac atc aag tac cga ggg cag	1392
Val Tyr Leu Phe Ser Val Gly Val Phe Asp Ile Lys Tyr Arg Gly Gln	
450 455 460	
tat cag aag tat gcg ctg ctg tgg atg gag agt gtg ccc tgc cgc ctg	1440
Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Pro Cys Arg Leu	
465 470 475 480	
ctg ggc ttc ctg gcc acg ctg tcc aca gag gtc tcg gtg ctg ctg ctg	1488
Leu Gly Phe Leu Ala Thr Leu Ser Thr Glu Val Ser Val Leu Leu Leu	
485 490 495	
aca ttc ctg acg ctg gag aag ttc ctt gtc ata gta ttc cct ttc agc	1536
Thr Phe Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe Ser	
500 505 510	
aac ctg cgc ctg ggc aag cgc cag act gct gtg gcc ctc gcc agc atc	1584
Asn Leu Arg Leu Gly Lys Arg Gln Thr Ala Val Ala Leu Ala Ser Ile	
515 520 525	
tgg gtg gtg gga ttt ctc ata gcg gcc gtt ccg ttc acc aga gag gat	1632
Trp Val Val Gly Phe Leu Ile Ala Ala Val Pro Phe Thr Arg Glu Asp	
530 535 540	
tat ttc ggc aac ttt tat ggg aaa aat gga gtc tgc ttc cca ctt cat	1680
Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu His	
545 550 555 560	
tat gac caa gca gaa gat ttt gga agt aga ggg tac tcc ctt ggg att	1728
Tyr Asp Gln Ala Glu Asp Phe Gly Ser Arg Gly Tyr Ser Leu Gly Ile	
565 570 575	
ttc cta ggt gtg aac ttg ctg gct ttc ctc gtc atc gtg att tcc tat	1776
Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Val Ile Val Ile Ser Tyr	
580 585 590	
gtc acc atg ttc tgc tcc att cat aaa aca gcc ctt cag act gca gaa	1824
Val Thr Met Phe Cys Ser Ile His Lys Thr Ala Leu Gln Thr Ala Glu	
595 600 605	
gtg agg agc cac atc ggg aag gag gtg gct gtt gca aac cgg ttc ttt	1872
Val Arg Ser His Ile Gly Lys Glu Val Ala Val Ala Asn Arg Phe Phe	
610 615 620	

FIG. 8D

ttt atc gtg ttc tct gat gcc atc tgc tgg atc cct gtg ttt gtc gtt	1920
Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val Val	
625 630 635 640	
aag atc ctg tct ctc ctt caa gtg gag ata cca ggc aca atc act tcc	1968
Lys Ile Leu Ser Leu Leu Gln Val Glu Ile Pro Gly Thr Ile Thr Ser	
645 650 655	
tgg atc gtg gtt ttt ttc ctt ccg gtg aac agc gcc tta aac ccc atc	2016
Trp Ile Val Val Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro Ile	
660 665 670	
ctc tac act ctg acg acc tcc ttt ttt aag gac aag ttg aaa cag ttg	2064
Leu Tyr Thr Leu Thr Thr Ser Phe Phe Lys Asp Lys Leu Lys Gln Leu	
675 680 685	
ctg cac aaa cat cgg agg aaa ccc atc ttc aaa gtt aag aag aaa agt	2112
Leu His Lys His Arg Arg Lys Pro Ile Phe Lys Val Lys Lys Lys Ser	
690 695 700	
tta tcc gct tcc att gtg tgg aca gac gag tct tca ctt aaa ctt gga	2160
Leu Ser Ala Ser Ile Val Trp Thr Asp Glu Ser Ser Leu Lys Leu Gly	
705 710 715 720	
gtg ttg agc aaa ata gcc ctt ggg gac agt ata atg aag ccg gtc tcc	2208
Val Leu Ser Lys Ile Ala Leu Gly Asp Ser Ile Met Lys Pro Val Ser	
725 730 735	
ccg tag	2214
Pro	

FIG. 9A

gac agc agt atg gtg gct cct ctg tgc ccc aaa ggg tat ttt ccc tgt	48
Asp Ser Ser Met Val Ala Pro Leu Cys Pro Lys Gly Tyr Phe Pro Cys	
1 5 10 15	
ggg aat ctc acc aaa tgc ttg ccc cga gcc ttt cac tgc gat ggt gtg	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Val	
20 25 30	
gat gat tgc ggg aat ggt gcc gac gag gac aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Asp Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg aca acc ata ttt ggc aca gtc cat ggg aat gtc aat aaa gtg	192
Gly Trp Thr Thr Ile Phe Gly Thr Val His Gly Asn Val Asn Lys Val	
50 55 60	
aca ttg aca cag gag tgc ttt ctc agc cag tat cca cag cac tgt tac	240
Thr Leu Thr Gln Glu Cys Phe Leu Ser Gln Tyr Pro Gln His Cys Tyr	
65 70 75 80	
tgc aga gaa aat gaa ctg gaa tgt gta aag gct gac tta aaa gct gtg	288
Cys Arg Glu Asn Glu Leu Glu Cys Val Lys Ala Asp Leu Lys Ala Val	
85 90 95	
cca aag gtt tcc agc aac gta aca tta cta tct ctt aag aaa aac aaa	336
Pro Lys Val Ser Ser Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac aga ctt cca gtc aag gtc ttc agc aga tac aca gaa ctc aga	384
Ile His Arg Leu Pro Val Lys Val Phe Ser Arg Tyr Thr Glu Leu Arg	
115 120 125	
aag ata tac ctt cag cac aac tgc atc aca cac atc tcc agg aga gca	432
Lys Ile Tyr Leu Gln His Asn Cys Ile Thr His Ile Ser Arg Arg Ala	
130 135 140	
ttc ctt gga tta cat aat cta caa ata ctg tat ctc agc cat aac tgc	480
Phe Leu Gly Leu His Asn Leu Gln Ile Leu Tyr Leu Ser His Asn Cys	
145 150 155 160	
att acc tct ctc agg cct ggg ata ttc aaa gac ttg cat cag ctt gct	528
Ile Thr Ser Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Ala	
165 170 175	
tgg cta att tta gat gac aac ccg atc acc aga atc tca cag aag tcc	576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Lys Ser	
180 185 190	
ttt atg ggg tta aac tcc ttg ttt ttc ttg tcc atg gtg ggt aac cgg	624
Phe Met Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Gly Asn Arg	
195 200 205	

FIG. 9B

ctc gag gcc ctt cct gaa aca ttg tgt gct cag atg cct caa ctc aac	672
Leu Glu Ala Leu Pro Glu Thr Leu Cys Ala Gln Met Pro Gln Leu Asn	
210 215 220	
tgg gtg gat ctg gca aac aat gga ata aag tac ata acg aac tcc acc	720
Trp Val Asp Leu Ala Asn Asn Gly Ile Lys Tyr Ile Thr Asn Ser Thr	
225 230 235 240	
ttc cta acg tgc gac tcg ctc acg gtt ctg ttt ctg cct aga aat caa	768
Phe Leu Thr Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln	
245 250 255	
att ggt ttt gtt cca gag aag aca ttt tct tca tta aaa aat tta gga	816
Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly	
260 265 270	
gaa ctg gac ctg tct agc aat atg ata aca aaa ctc cca gtc cac ctt	864
Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro Val His Leu	
275 280 285	
ttc agc gac ctt cat ctt ctc cag aag ctg aac ctg tca tcc aac cct	912
Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro	
290 295 300	
ctt ctg tat gtc cac aag aac cag ttt gga agt ctc aaa caa ctt cag	960
Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys Gln Leu Gln	
305 310 315 320	
tct cta gac ctg gaa agg ata gag att cca aac ata agc aca gga atg	1008
Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Ser Thr Gly Met	
325 330 335	
ttc cag cca atg aag aac ctt tct cac att tat ttg aaa acc ttt cga	1056
Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Leu Lys Thr Phe Arg	
340 345 350	
tac tgc tcc tat gtc ccc cat gtc cga atc tgt atg ccg tcg act gat	1104
Tyr Cys Ser Tyr Val Pro His Val Arg Ile Cys Met Pro Ser Thr Asp	
355 360 365	
ggt att tct tcg tct gag gac ctc ttg gct aac ggt	1140
Gly Ile Ser Ser Ser Glu Asp Leu Leu Ala Asn Gly	
370 375 380	

FIG. 10A

1 MIVFLVFKHLESLRLITMFFLLHFIVLINVKDFALTQGSMTIPSCQKGYF 50
 . | : || | | . | : | ||
 1MTSGSVFFYILIFGKYFSHGGGQDV..KCSLGYF 32

51 PCGNLTCKLPRAFHCDGKDDCGNGADEENCGDTSGWATIFGTVHGNANSV 100
 ||||:|||||. ||. | |||| | ||:|||| . ||. |
 33 PCGNITCKLPQLLHCNGVDDCGNQADEDNCGDNNGWSMQFDKYFASYK 82

101ALTQECFLKQYPQCCCKETELECNGDLKSVPMISNNVTLLS 143
 | | || . | | | . ||:| . |: || : | || : |
 83 TSQYPFEAETPECLVGSVPVQCLCQGLELDCDETNLRAVPSVSSNVTAMS 132

144 LKKNKIHSLEPDKVFIKYTKLKKIFLQHNCIRHISRKAFFGLCNLQILYLN 193
 | . | | | | | | | . |: ||. | | | | | | . | |||
 133 LQWNLIRKLPPDCFKNYHDLQKLYLQNNKITSISIIYAFRGLNSLTCLYLS 182

194 HNCITTLRPGIFKDLHQLTWLIILDDNPITRISQRLFTGLNSLFFLSMVNN 243
 | | | | |: ||: |. |||. | |||: || :. || | |||| | :. ||
 183 HNRITFLKPGVFEDLHRLEWLIIEDNHLRSISPPTFYGLNSLILLVLMNN 232

244 YLEALP.KQMCQMPQLNWVDLEGNRIKYLTNSTFLSCDSLTVLFLPRNQ 292
 | | | : | ||. |. |||| | | | ||: || . |||| : : |
 233 VLTRLDPKPLCQHMPRLHWLDLEGNHINLRNLTFISCSNLTVLVMRKNK 282

293 IGFVPEKTFSSLKNLGELDLSSNTITELSPHLFKDLKLLQKLNLSNPLM 342
 | . | ||. | . | |||| | | | | : |||| | . |||| ||:
 283 INHLNENTFAPLQKLDLGLSGNKIENLPPLIFKDLKELSQNLNSYNPIQ 332

343 YLHKNQFESLKQLQSLDLERIEIPNINTRMFQPMKNLSHIYFKNFRYCSY 392
 : |||: | . |. || | | | | | | |||. |: ||||| |. || |
 333 KIQANQFDYLVKLKSLSLEGIEISNIQORMFRPLMNLSHIYFKKFQYCGY 382

393 APHVRICMPLTDGISSFEDLLANNILRIFVWVIAFITCFGNLFVIGMRSF 442
 |||| | | |||| |. |||. | |: ||||. : ||||: || | | :
 383 APHVRCKPNTDGISSLENLLASIIQRVFVWVSAVTCFGNIFVICMRPY 432

443 IKAENTTHAMSIKILCCADCLMGVYLFFVGIFDIKYRGQYQKYALLWMES 492
 |: || : || | ||||| ||: || : | ||: ||: | |: | ||||
 433 IRSENKLYAMSIISLCCADCLMGIYLFVIGGFDLKFRGEYNKHAQLWMES 482

493 VQCRLMGFLAMLSTEVSVLLLTLYLTLEKFLVIVFPFSNIRPGKRQTSVIL 542
 |. |. | ||. ||||| |||||: ||||: | ||: || : |||| . | : |
 483 THCQLVGLAILSTEVSVLLLTFLTLEKYICIVYFPFCVRPGKCRITITVL 532

```

543 ICIWMAGFLIAVIFPNKDYFGNFYGKNVCFLPYDQTEDIGSKGYSLG 592
| | . | : : | | | : : | : | | | | : : | | | . | |
533 ILIWITGFIVAFIPLSNKEFFKNYYGTNGVCFPLHSEDTESIGAQIYSVA 582

593 IFLGVNLLAFLIIIVFSYITMFCSIQKTALQTTEVRNCFGREAVANRFFF 642
| | : | | : | | | . | | | : . . : | : | | : | . . | | |
583 IFLGINLAAFIIIIVFSYGSMFYSVHQSAITATEIRNQVKKEMILAKRFFF 632

643 IVFSDAICWIPVFVVVKILSLFRVEIPDTMTSWIVIFFLPVNSALNPILYT 692
| | . | : : | | : | | | | | | | | | | | | | | | | | |
633 IVFTDALCWIFIPIFVVKFLSLLQVEIPGTITSWWVIFILPINSALNPILYT 682

693 LTTNFFKDCLKQLLHKH.QRKSIKFIKKKSLSTSIVWIEDSSSLKLGLVN 741
| | | | : : . : : | | | . . | . . | : : | : : |
683 LTTRPFKEMIHRFWYNRYQRKSMDSKGQKTYAPSFIVWE.....MWPLQ 726

742 KITLGDSIMKPVS..... 754
. : : | |
727 E..MPPELMKPDLFITYPCEMSLISQSTRLN SYS 757
```


[illegible]

FIG. 11B

551 KGYSLGIFLGVNLLAFLIIVFSYITMFCSIQKTALQTEVRNCFGREVAV 600
:|||||:|||||:|||||:|||||:|||||:|||||:|||||:|||||
551 RGYSLGIFLGVNLLAFLVIVISYVTMFCSIHKTALQAEVRSHIGKEVAV 600

601 ANRFFFIVFSDAICWIPVFVVKILSLFRVEIPDTMTSWIVIFFLPVNSAL 650
|||||:|||||:|||||:|||||:|||||:|||||:|||||:|||||
601 ANRFFFIVFSDAICWIPVFVVKILSLLQVEIPGTITSWIVVFFLPVNSAL 650

651 NPILYTLTTFKDKLKQLLHKHQRKSIFKIKKKSLSTSIVWIEDSSSLK 700
|||||:|||||:|||||:|||||:|||||:|||||:|||||:|||||
651 NPILYTLTTSFFKDKLKQLLHKHRRKPIFKVKKKSLSASIVW.TDESSLK 699

701 LGVLNKITLGDSIMKPVS.. 718
||||:|||||
700 LGVLSKIALGDSIMKPVSP 718

[illegible]

SEQUENCE LISTING

<110> Paszty, Christopher J.
Gong, Jianhua
Daugherty, Betsy
Rogers, Norma

<120> Leucine-Rich G Protein Coupled Receptor-8 Molecules and
Uses Thereof

<130> 00-1229-A

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<150> 60/224,455

<151> 2000-08-10

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<170> PatentIn Ver. 2.0

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<213> Homo sapiens

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<221> sig_peptide

<222> (1)..(108)

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atg att gtt ttt ctg gtt ttt aaa cat ctc ttc agc ctc aga ttg att	48
Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile	
1 5 10 15	
aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat	96
Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp	
20 25 30	
ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga	144
Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly	
35 40 45	
tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac	192
Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His	
50 55 60	
tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt	240
Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys	
65 70 75 80	
ggg gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336

Ala	Asn	Ser	Val	Ala	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Lys	Gln	Tyr	Pro	
			100					105					110			
caa	tgc	tgt	gac	tgc	aaa	gaa	act	gaa	ttg	gaa	tgt	gta	aat	ggg	gac	384
Gln	Cys	Cys	Asp	Cys	Lys	Glu	Thr	Glu	Leu	Glu	Cys	Val	Asn	Gly	Asp	
		115					120					125				
tta	aag	tct	gtg	cgc	atg	att	tct	aac	aat	gtg	aca	tta	ctg	tct	ctt	432
Leu	Lys	Ser	Val	Pro	Met	Ile	Ser	Asn	Asn	Val	Thr	Leu	Leu	Ser	Leu	
	130					135					140					
aag	aaa	aac	aaa	atc	cac	agt	ctt	cca	gat	aaa	ggt	ttc	atc	aaa	tac	480
Lys	Lys	Asn	Lys	Ile	His	Ser	Leu	Pro	Asp	Lys	Val	Phe	Ile	Lys	Tyr	
145					150					155					160	
aca	aaa	ctt	aaa	aag	ata	ttt	ctt	cag	cat	aat	tgc	att	aga	cac	ata	528
Thr	Lys	Leu	Lys	Lys	Ile	Phe	Leu	Gln	His	Asn	Cys	Ile	Arg	His	Ile	
				165				170						175		
tcc	agg	aaa	gca	ttt	ttt	gga	tta	tgt	aat	ctg	caa	ata	tta	tat	ctc	576
Ser	Arg	Lys	Ala	Phe	Phe	Gly	Leu	Cys	Asn	Leu	Gln	Ile	Leu	Tyr	Leu	
			180					185					190			
aac	cac	aac	tgc	atc	aca	acc	ctc	aga	cct	gga	ata	ttc	aaa	gac	tta	624
Asn	His	Asn	Cys	Ile	Thr	Thr	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu	
		195					200					205				
cat	cag	cta	act	tgg	cta	att	cta	gat	gac	aat	cca	ata	acc	aga	att	672
His	Gln	Leu	Thr	Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile	
	210					215					220					
tca	cag	cgc	ttg	ttt	acg	gga	tta	aat	tcc	ttg	ttt	ttc	ctg	tct	atg	720
Ser	Gln	Arg	Leu	Phe	Thr	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met	
225					230					235					240	
ggt	aat	aac	tac	tta	gaa	gct	ctt	ccc	aag	cag	atg	tgt	gcc	caa	atg	768
Val	Asn	Asn	Tyr	Leu	Glu	Ala	Leu	Pro	Lys	Gln	Met	Cys	Ala	Gln	Met	
				245				250						255		
cct	caa	ctc	aac	tgg	gtg	gat	ttg	gaa	ggc	aat	aga	ata	aag	tat	ctc	816
Pro	Gln	Leu	Asn	Trp	Val	Asp	Leu	Glu	Gly	Asn	Arg	Ile	Lys	Tyr	Leu	
			260					265					270			
aca	aat	tct	acg	ttt	ctg	tcg	tgc	gat	tcg	ctc	aca	gtg	ctg	ttt	ctg	864
Thr	Asn	Ser	Thr	Phe	Leu	Ser	Cys	Asp	Ser	Leu	Thr	Val	Leu	Phe	Leu	
		275					280					285				
cct	aga	aat	caa	att	ggg	ttt	ggt	cca	gag	aag	aca	ttt	tct	tca	tta	912
Pro	Arg	Asn	Gln	Ile	Gly	Phe	Val	Pro	Glu	Lys	Thr	Phe	Ser	Ser	Leu	
	290					295					300					
aaa	aat	tta	gga	gaa	ctg	gat	ctg	tct	agc	aat	acg	ata	acg	gag	cta	960
Lys	Asn	Leu	Gly	Glu	Leu	Asp	Leu	Ser	Ser	Asn	Thr	Ile	Thr	Glu	Leu	
305					310					315					320	
tca	cct	cac	ctt	ttt	aaa	gac	ttg	aag	ctt	cta	caa	aag	ctg	aac	ctg	1008
Ser	Pro	His	Leu	Phe	Lys	Asp	Leu	Lys	Leu	Leu	Gln	Lys	Leu	Asn	Leu	
				325					330					335		
tca	tcc	aat	cct	ctt	atg	tat	ctt	cac	aag	aac	cag	ttt	gaa	agt	ctt	1056
Ser	Ser	Asn	Pro	Leu	Met	Tyr	Leu	His	Lys	Asn	Gln	Phe	Glu	Ser	Leu	

340	345	350	
aaa caa ctt cag tct cta gac ctg gaa agg ata gag att cca aat ata Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile 355 360 365			1104
aac aca cga atg ttt caa ccc atg aag aat ctt tct cac att tat ttc Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Phe 370 375 380			1152
aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc cga ata tgt atg Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met 385 390 395 400			1200
ccc ttg acg gac ggc att tct tca ttt gag gac ctc ttg gct aac aat Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn Asn 405 410 415			1248
atc ctc aga ata ttt gtc tgg gtt ata gct ttc att acc tgc ttt gga Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe Gly 420 425 430			1296
aat ctt ttt gtc att ggc atg aga tct ttc att aaa gct gaa aat aca Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn Thr 435 440 445			1344
act cac gct atg tcc atc aaa atc ctt tgt tgt gct gat tgc ctg atg Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met 450 455 460			1392
ggt gtt tac ttg ttc ttt gtt ggc att ttc gat ata aaa tac cga ggg Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg Gly 465 470 475 480			1440
cag tat cag aag tat gcc ttg ctg tgg atg gag agc gtg cag tgc cgc Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys Arg 485 490 495			1488
ctc atg ggg ttc ctg gcc atg ctg tcc acc gaa gtc tct gtt ctg cta Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu Leu 500 505 510			1536
ctg acc tac ttg act ttg gag aag ttc ctg gtc att gtc ttc ccc ttc Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe 515 520 525			1584
agt aac att cga cct gga aaa cgg cag acc tca gtc atc ctc att tgc Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile Cys 530 535 540			1632
atc tgg atg gcg gga ttt tta ata gct gta att cca ttt tgg aat aag Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn Lys 545 550 555 560			1680
gat tat ttt gga aac ttt tat ggg aaa aat gga gta tgt ttc cca ctt Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu 565 570 575			1728
tat tat gac caa aca gaa gat att gga agc aaa ggg tat tct ctt gga Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu Gly 580 585 590			1776

att ttc cta ggt gtg aac ttg ctg gct ttt ctc atc att gtg ttt tcc 1824
 Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe Ser
 595 600 605
 tat att act atg ttc tgt tcc att caa aaa acc gcc ttg cag acc aca 1872
 Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr Thr
 610 615 620
 gaa gta agg aat tgt ttt gga aga gag gtg gct gtt gca aat cgt ttc 1920
 Glu Val Arg Asn Cys Phe Gly Arg Glu Val Ala Val Ala Asn Arg Phe
 625 630 635 640
 ttt ttt ata gtg ttc tct gat gcc atc tgc tgg att cct gta ttt gta 1968
 Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val
 645 650 655
 gtt aaa atc ctt tcc ctc ttc cgg gtg gaa ata cca gac aca atg act 2016
 Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro Asp Thr Met Thr
 660 665 670
 tcc tgg ata gtg att ttt ttc ctt cca gtt aac agt gct ttg aat cca 2064
 Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro
 675 680 685
 atc ctc tat act ctc aca acc aac ttt ttt aag gac aag ttg aaa cag 2112
 Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp Lys Leu Lys Gln
 690 695 700
 ctg ctg cac aaa cat cag agg aaa tca att ttc aaa att aaa aaa aaa 2160
 Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys Ile Lys Lys Lys
 705 710 715 720
 agt tta tct aca tcc att gtg tgg ata gag gac tcc tct tcc ctg aaa 2208
 Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser Ser Ser Leu Lys
 725 730 735
 ctt ggg gtt ttg aac aaa ata aca ctt gga gac agt ata atg aaa cca 2256
 Leu Gly Val Leu Asn Lys Ile Thr Leu Gly Asp Ser Ile Met Lys Pro
 740 745 750
 gtt tcc tag 2265
 Val Ser

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 Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp
 20 25 30
 Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45
 Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His

50					55					60					
Cys	Asp	Gly	Lys	Asp	Asp	Cys	Gly	Asn	Gly	Ala	Asp	Glu	Glu	Asn	Cys
65					70					75					80
Gly	Asp	Thr	Ser	Gly	Trp	Ala	Thr	Ile	Phe	Gly	Thr	Val	His	Gly	Asn
				85					90					95	
Ala	Asn	Ser	Val	Ala	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Lys	Gln	Tyr	Pro
			100					105					110		
Gln	Cys	Cys	Asp	Cys	Lys	Glu	Thr	Glu	Leu	Glu	Cys	Val	Asn	Gly	Asp
		115					120					125			
Leu	Lys	Ser	Val	Pro	Met	Ile	Ser	Asn	Asn	Val	Thr	Leu	Leu	Ser	Leu
		130				135					140				
Lys	Lys	Asn	Lys	Ile	His	Ser	Leu	Pro	Asp	Lys	Val	Phe	Ile	Lys	Tyr
145					150					155					160
Thr	Lys	Leu	Lys	Lys	Ile	Phe	Leu	Gln	His	Asn	Cys	Ile	Arg	His	Ile
				165					170					175	
Ser	Arg	Lys	Ala	Phe	Phe	Gly	Leu	Cys	Asn	Leu	Gln	Ile	Leu	Tyr	Leu
			180					185					190		
Asn	His	Asn	Cys	Ile	Thr	Thr	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu
		195					200					205			
His	Gln	Leu	Thr	Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile
	210					215					220				
Ser	Gln	Arg	Leu	Phe	Thr	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met
225						230					235				240
Val	Asn	Asn	Tyr	Leu	Glu	Ala	Leu	Pro	Lys	Gln	Met	Cys	Ala	Gln	Met
				245					250					255	
Pro	Gln	Leu	Asn	Trp	Val	Asp	Leu	Glu	Gly	Asn	Arg	Ile	Lys	Tyr	Leu
			260					265					270		
Thr	Asn	Ser	Thr	Phe	Leu	Ser	Cys	Asp	Ser	Leu	Thr	Val	Leu	Phe	Leu
		275					280					285			
Pro	Arg	Asn	Gln	Ile	Gly	Phe	Val	Pro	Glu	Lys	Thr	Phe	Ser	Ser	Leu
	290					295					300				
Lys	Asn	Leu	Gly	Glu	Leu	Asp	Leu	Ser	Ser	Asn	Thr	Ile	Thr	Glu	Leu
305						310					315				320
Ser	Pro	His	Leu	Phe	Lys	Asp	Leu	Lys	Leu	Gln	Lys	Leu	Asn	Leu	
				325					330				335		
Ser	Ser	Asn	Pro	Leu	Met	Tyr	Leu	His	Lys	Asn	Gln	Phe	Glu	Ser	Leu
			340					345					350		
Lys	Gln	Leu	Gln	Ser	Leu	Asp	Leu	Glu	Arg	Ile	Glu	Ile	Pro	Asn	Ile
		355					360					365			
Asn	Thr	Arg	Met	Phe	Gln	Pro	Met	Lys	Asn	Leu	Ser	His	Ile	Tyr	Phe
						375					380				

Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met
 385 390 395 400
 Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn Asn
 405 410 415
 Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe Gly
 420 425 430
 Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn Thr
 435 440 445
 Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met
 450 455 460
 Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg Gly
 465 470 475 480
 Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys Arg
 485 490 495
 Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu Leu
 500 505 510
 Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe
 515 520 525
 Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile Cys
 530 535 540
 Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn Lys
 545 550 555 560
 Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu
 565 570 575
 Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu Gly
 580 585 590
 Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe Ser
 595 600 605
 Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr Thr
 610 615 620
 Glu Val Arg Asn Cys Phe Gly Arg Glu Val Ala Val Ala Asn Arg Phe
 625 630 635 640
 Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val
 645 650 655
 Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro Asp Thr Met Thr
 660 665 670
 Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro
 675 680 685
 Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp Lys Leu Lys Gln
 690 695 700

Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys Ile Lys Lys Lys
 705 710 715 720

Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser Ser Ser Leu Lys
 725 730 735

Leu Gly Val Leu Asn Lys Ile Thr Leu Gly Asp Ser Ile Met Lys Pro
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Val Ser

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 <213> Homo sapiens

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Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser
 35 40 45

Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60

Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80

Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95

Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110

Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125

Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140

Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys
 145 150 155 160

Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr
 165 170 175

Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu
 180 185 190

Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr
 195 200 205

Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn
 210 215 220

Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr
 225 230 235 240
 Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln
 245 250 255
 Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly
 260 265 270
 Glu Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu
 275 280 285
 Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro
 290 295 300
 Leu Met Tyr Leu His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln
 305 310 315 320
 Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met
 325 330 335
 Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg
 340 345 350
 Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp
 355 360 365
 Gly Ile Ser Ser Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg Ile
 370 375 380
 Phe Val Trp Val Ile Ala Phe Ile Thr Cys Phe Gly Asn Leu Phe Val
 385 390 395 400
 Ile Gly Met Arg Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met
 405 410 415
 Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met Gly Val Tyr Leu
 420 425 430
 Phe Phe Val Gly Ile Phe Asp Ile Lys Tyr Arg Gly Gln Tyr Gln Lys
 435 440 445
 Tyr Ala Leu Leu Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe
 450 455 460
 Leu Ala Met Leu Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu
 465 470 475 480
 Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg
 485 490 495
 Pro Gly Lys Arg Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala
 500 505 510
 Gly Phe Leu Ile Ala Val Ile Pro Phe Trp Asn Lys Asp Tyr Phe Gly
 515 520 525
 Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu Tyr Tyr Asp Gln
 530 535 540
 Thr Glu Asp Ile Gly Ser Lys Gly Tyr Ser Leu Gly Ile Phe Leu Gly

545 550 555 560

Val Asn Leu Leu Ala Phe Leu Ile Ile Val Phe Ser Tyr Ile Thr Met
565 570 575

Phe Cys Ser Ile Gln Lys Thr Ala Leu Gln Thr Thr Glu Val Arg Asn
580 585 590

Cys Phe Gly Arg Glu Val Ala Val Ala Asn Arg Phe Phe Phe Ile Val
595 600 605

Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val Val Lys Ile Leu
610 615 620

Ser Leu Phe Arg Val Glu Ile Pro Asp Thr Met Thr Ser Trp Ile Val
625 630 635 640

Ile Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr
645 650 655

Leu Thr Thr Asn Phe Phe Lys Asp Lys Leu Lys Gln Leu Leu His Lys
660 665 670

His Gln Arg Lys Ser Ile Phe Lys Ile Lys Lys Lys Ser Leu Ser Thr
675 680 685

Ser Ile Val Trp Ile Glu Asp Ser Ser Ser Leu Lys Leu Gly Val Leu
690 695 700

Asn Lys Ile Thr Leu Gly Asp Ser Ile Met Lys Pro Val Ser
705 710 715

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<220>
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ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys	
20 25 30	
gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg	192
Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val	
50 55 60	
gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac	240
Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp	

65	70	75	80	
tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg				288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val				
	85	90	95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa				336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys				
	100	105	110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa				384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys				
	115	120	125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca				432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala				
	130	135	140	
ttt ttt gga tta tgt aat ctg caa ata tta tat ctc aac cac aac tgc				480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys				
	145	150	155	160
atc aca acc ctc aga cct gga ata ttc aaa gac tta cat cag cta act				528
Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr				
	165	170	175	
tgg cta att cta gat gac aat cca ata acc aga att tca cag cgc ttg				576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu				
	180	185	190	
ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac				624
Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr				
	195	200	205	
tta gaa gct ctt ccc aag cag atg tgt gcc caa atg cct caa ctc aac				672
Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn				
	210	215	220	
tgg gtg gat ttg gaa ggc aat aga ata aag tat ctc aca aat tct acg				720
Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr				
	225	230	235	240
ttt ctg tcg tgc gat tcg ctc aca gtg ctg ttt ctg cct aga aat caa				768
Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln				
	245	250	255	
att ggt ttt gtt cca gag aag aca ttt tct tca tta aaa aat tta gga				816
Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly				
	260	265	270	
gaa ctg gat ctg tct agc aat acg ata acg gag cta tca cct cac ctt				864
Glu Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu				
	275	280	285	
ttt aaa gac ttg aag ctt cta caa aag ctg aac ctg tca tcc aat cct				912
Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro				
	290	295	300	
ctt atg tat ctt cac aag aac cag ttt gaa agt ctt aaa caa ctt cag				960
Leu Met Tyr Leu His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln				
	305	310	315	320

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 Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met
 325 330 335

ttt caa ccc atg aag aat ctt tct cac att tat ttc aaa aac ttt cga 1056
 Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg
 340 345 350

tac tgc tcc tat gct ccc cat gtc cga ata tgt atg ccc ttg acg gac 1104
 Tyr Cys Ser Tyr Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp
 355 360 365

ggc att tct tca ttt gag gac ctc ttg gct aac aat atc ctc aga 1149
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 370 375 380

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<212> PRT

<213> Homo sapiens

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Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser
 35 40 45

Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60

Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80

Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95

Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110

Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125

Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140

Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys
 145 150 155 160

Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr
 165 170 175

Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu
 180 185 190

Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr

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Leu	Glu	Ala	Leu	Pro	Lys	Gln	Met	Cys	Ala	Gln	Met	Pro	Gln	Leu	Asn
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Trp	Val	Asp	Leu	Glu	Gly	Asn	Arg	Ile	Lys	Tyr	Leu	Thr	Asn	Ser	Thr
225					230					235					240
Phe	Leu	Ser	Cys	Asp	Ser	Leu	Thr	Val	Leu	Phe	Leu	Pro	Arg	Asn	Gln
				245					250					255	
Ile	Gly	Phe	Val	Pro	Glu	Lys	Thr	Phe	Ser	Ser	Leu	Lys	Asn	Leu	Gly
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Glu	Leu	Asp	Leu	Ser	Ser	Asn	Thr	Ile	Thr	Glu	Leu	Ser	Pro	His	Leu
		275					280					285			
Phe	Lys	Asp	Leu	Lys	Leu	Leu	Gln	Lys	Leu	Asn	Leu	Ser	Ser	Asn	Pro
	290					295					300				
Leu	Met	Tyr	Leu	His	Lys	Asn	Gln	Phe	Glu	Ser	Leu	Lys	Gln	Leu	Gln
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Ser	Leu	Asp	Leu	Glu	Arg	Ile	Glu	Ile	Pro	Asn	Ile	Asn	Thr	Arg	Met
				325					330					335	
Phe	Gln	Pro	Met	Lys	Asn	Leu	Ser	His	Ile	Tyr	Phe	Lys	Asn	Phe	Arg
			340					345					350		
Tyr	Cys	Ser	Tyr	Ala	Pro	His	Val	Arg	Ile	Cys	Met	Pro	Leu	Thr	Asp
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Thr	Met	Phe	Phe	Leu	Leu	His	Phe	Ile	Val	Leu	Ile	Asn	Val	Lys	Asp	
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ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga															144	
Phe	Ala	Leu	Thr	Gln	Gly	Ser	Met	Ile	Thr	Pro	Ser	Cys	Gln	Lys	Gly	
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tat	ttt	ccc	tgt	ggg	aat	ctt	acc	aag	tgc	tta	ccc	cga	gct	ttt	cac	192
Tyr	Phe	Pro	Cys	Gly	Asn	Leu	Thr	Lys	Cys	Leu	Pro	Arg	Ala	Phe	His	
	50					55					60					
tgt	gat	ggc	aag	gat	gac	tgt	ggg	aac	ggg	gcg	gac	gaa	gag	aac	tgt	240
Cys	Asp	Gly	Lys	Asp	Asp	Cys	Gly	Asn	Gly	Ala	Asp	Glu	Glu	Asn	Cys	
65				70				75						80		
ggg	gac	act	agt	gga	tgg	gcg	acc	ata	ttt	ggc	aca	gtg	cat	gga	aat	288
Gly	Asp	Thr	Ser	Gly	Trp	Ala	Thr	Ile	Phe	Gly	Thr	Val	His	Gly	Asn	
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gct	aac	agc	gtg	gcc	tta	aca	cag	gag	tgc	ttt	cta	aaa	cag	tat	cca	336
Ala	Asn	Ser	Val	Ala	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Lys	Gln	Tyr	Pro	
			100				105						110			
caa	tgc	tgt	gac	tgc	aaa	gaa	act	gaa	ttg	gaa	tgt	gta	aat	ggg	gac	384
Gln	Cys	Cys	Asp	Cys	Lys	Glu	Thr	Glu	Leu	Glu	Cys	Val	Asn	Gly	Asp	
		115				120						125				
tta	aag	tct	gtg	ccg	atg	att	tct	aac	aat	gtg	aca	tta	ctg	tct	ctt	432
Leu	Lys	Ser	Val	Pro	Met	Ile	Ser	Asn	Asn	Val	Thr	Leu	Leu	Ser	Leu	
	130					135					140					
aag	aaa	aac	aaa	atc	cac	agt	ctt	cca	gat	aaa	gtt	ttc	atc	aaa	tac	480
Lys	Lys	Asn	Lys	Ile	His	Ser	Leu	Pro	Asp	Lys	Val	Phe	Ile	Lys	Tyr	
145				150						155					160	
aca	aaa	ctt	aaa	aag	ata	ttt	ctt	cag	cat	aat	tgc	att	aga	cac	ata	528
Thr	Lys	Leu	Lys	Lys	Ile	Phe	Leu	Gln	His	Asn	Cys	Ile	Arg	His	Ile	
				165				170						175		
tcc	agg	aaa	gca	ttt	ttt	gga	tta	tgt	aat	ctg	caa	ata	tta	tat	ctc	576
Ser	Arg	Lys	Ala	Phe	Phe	Gly	Leu	Cys	Asn	Leu	Gln	Ile	Leu	Tyr	Leu	
			180					185					190			
aac	cac	aac	tgc	atc	aca	acc	ctc	aga	cct	gga	ata	ttc	aaa	gac	tta	624
Asn	His	Asn	Cys	Ile	Thr	Thr	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu	
		195					200					205				
cat	cag	cta	act	tgg	cta	att	cta	gat	gac	aat	cca	ata	acc	aga	att	672
His	Gln	Leu	Thr	Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile	
	210					215					220					
tca	cag	cgc	ttg	ttt	acg	gga	tta	aat	tcc	ttg	ttt	ttc	ctg	tct	atg	720
Ser	Gln	Arg	Leu	Phe	Thr	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met	
225					230				235						240	
gtt	aat	aac	tac	tta	gaa	gct	ctt	ccc	aag	cag	atg	tgt	gcc	caa	atg	768
Val	Asn	Asn	Tyr	Leu	Glu	Ala	Leu	Pro	Lys	Gln	Met	Cys	Ala	Gln	Met	
				245				250						255		
cct	caa	ctc	aac	tgg	gtg	gat	ttg	gaa	ggc	aat	aga	ata	aag	tat	ctc	816
Pro	Gln	Leu	Asn	Trp	Val	Asp	Leu	Glu	Gly	Asn	Arg	Ile	Lys	Tyr	Leu	
			260					265					270			
aca	aat	tct	acg	ttt	ctg	tcg	tgc	gat	tcg	ctc	aca	gtg	ctg	gat	ctg	864
Thr	Asn	Ser	Thr	Phe	Leu	Ser	Cys	Asp	Ser	Leu	Thr	Val	Leu	Asp	Leu	
		275					280					285				

tct agc aat acg ata acg gag cta tca cct cac ctt ttt aaa gac ttg	912
Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu	
290 295 300	
aag ctt cta caa aag ctg aac ctg tca tcc aat cct ctt atg tat ctt	960
Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu	
305 310 315 320	
cac aag aac cag ttt gaa agt ctt aaa caa ctt cag tct cta gac ctg	1008
His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu	
325 330 335	
gaa agg ata gag att cca aat ata aac aca cga atg ttt caa ccc atg	1056
Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met	
340 345 350	
aag aat ctt tct cac att tat ttc aaa aac ttt cga tac tgc tcc tat	1104
Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr	
355 360 365	
gct ccc cat gtc cga ata tgt atg ccc ttg acg gac ggc att tct tca	1152
Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser	
370 375 380	
ttt gag gac ctc ttg gct aac aat atc ctc aga ata ttt gtc tgg gtt	1200
Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val	
385 390 395 400	
ata gct ttc att acc tgc ttt gga aat ctt ttt gtc att ggc atg aga	1248
Ile Ala Phe Ile Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg	
405 410 415	
tct ttc att aaa gct gaa aat aca act cac gct atg tcc atc aaa atc	1296
Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile	
420 425 430	
ctt tgt tgt gct gat tgc ctg atg ggt gtt tac ttg ttc ttt gtt ggc	1344
Leu Cys Cys Ala Asp Cys Leu Met Gly Val Tyr Leu Phe Phe Val Gly	
435 440 445	
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Ile Phe Asp Ile Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu	
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tgg atg gag agc gtg cag tgc cgc ctc atg ggg ttc ctg gcc atg ctg	1440
Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu	
465 470 475 480	
tcc acc gaa gtc tct gtt ctg cta ctg acc tac ttg act ttg gag aag	1488
Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu Glu Lys	
485 490 495	
ttc ctg gtc att gtc ttc ccc ttc agt aac att cga cct gga aaa cgg	1536
Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg Pro Gly Lys Arg	
500 505 510	
cag acc tca gtc atc ctc att tgc atc tgg atg gcg gga ttt tta ata	1584
Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala Gly Phe Leu Ile	
515 520 525	
gct gta att cca ttt tgg aat aag gat tat ttt gga aac ttt tat ggg	1632

Ala	Val	Ile	Pro	Phe	Trp	Asn	Lys	Asp	Tyr	Phe	Gly	Asn	Phe	Tyr	Gly	
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aaa	aat	gga	gta	tgt	ttc	cca	ctt	tat	tat	gac	caa	aca	gaa	gat	att	1680
Lys	Asn	Gly	Val	Cys	Phe	Pro	Leu	Tyr	Tyr	Asp	Gln	Thr	Glu	Asp	Ile	
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gga	agc	aaa	ggg	tat	tct	ctt	gga	att	ttc	cta	ggg	gtg	aac	ttg	ctg	1728
Gly	Ser	Lys	Gly	Tyr	Ser	Leu	Gly	Ile	Phe	Leu	Gly	Val	Asn	Leu	Leu	
				565					570					575		
gct	ttt	ctc	atc	att	gtg	ttt	tcc	tat	att	act	atg	ttc	tgt	tcc	att	1776
Ala	Phe	Leu	Ile	Ile	Val	Phe	Ser	Tyr	Ile	Thr	Met	Phe	Cys	Ser	Ile	
			580					585					590			
caa	aaa	acc	gcc	ttg	cag	acc	aca	gaa	gta	agg	aat	tgt	ttt	gga	aga	1824
Gln	Lys	Thr	Ala	Leu	Gln	Thr	Thr	Glu	Val	Arg	Asn	Cys	Phe	Gly	Arg	
		595					600					605				
gag	gtg	gct	gtt	gca	aat	cgt	ttc	ttt	ttt	ata	gtg	ttc	tct	gat	gcc	1872
Glu	Val	Ala	Val	Ala	Asn	Arg	Phe	Phe	Phe	Ile	Val	Phe	Ser	Asp	Ala	
610						615					620					
atc	tgc	tgg	att	cct	gta	ttt	gta	gtt	aaa	atc	ctt	tcc	ctc	ttc	cgg	1920
Ile	Cys	Trp	Ile	Pro	Val	Phe	Val	Val	Lys	Ile	Leu	Ser	Leu	Phe	Arg	
625					630					635					640	
gtg	gaa	ata	cca	gac	aca	atg	act	tcc	tgg	ata	gtg	att	ttt	ttc	ctt	1968
Val	Glu	Ile	Pro	Asp	Thr	Met	Thr	Ser	Trp	Ile	Val	Ile	Phe	Phe	Leu	
				645					650					655		
cca	gtt	aac	agt	gct	ttg	aat	cca	atc	ctc	tat	act	ctc	aca	acc	aac	2016
Pro	Val	Asn	Ser	Ala	Leu	Asn	Pro	Ile	Leu	Tyr	Thr	Leu	Thr	Thr	Asn	
			660					665					670			
ttt	ttt	aag	gac	aag	ttg	aaa	cag	ctg	ctg	cac	aaa	cat	cag	agg	aaa	2064
Phe	Phe	Lys	Asp	Lys	Leu	Lys	Gln	Leu	Leu	His	Lys	His	Gln	Arg	Lys	
		675					680					685				
tca	att	ttc	aaa	att	aaa	aaa	aaa	agt	tta	tct	aca	tcc	att	gtg	tgg	2112
Ser	Ile	Phe	Lys	Ile	Lys	Lys	Lys	Ser	Leu	Ser	Thr	Ser	Ile	Val	Trp	
690						695					700					
ata	gag	gac	tcc	tct	tcc	ctg	aaa	ctt	ggg	gtt	ttg	aac	aaa	ata	aca	2160
Ile	Glu	Asp	Ser	Ser	Ser	Leu	Lys	Leu	Gly	Val	Leu	Asn	Lys	Ile	Thr	
705					710				715					720		
ctt	gga	gac	agt	ata	atg	aaa	cca	gtt	tcc	tag						2193
Leu	Gly	Asp	Ser	Ile	Met	Lys	Pro	Val	Ser							
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 Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45
 Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His
 50 55 60
 Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys
 65 70 75 80
 Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn
 85 90 95
 Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro
 100 105 110
 Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp
 115 120 125
 Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu
 130 135 140
 Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr
 145 150 155 160
 Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile
 165 170 175
 Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu
 180 185 190
 Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu
 195 200 205
 His Gln Leu Thr Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile
 210 215 220
 Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met
 225 230 235 240
 Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met
 245 250 255
 Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu
 260 265 270
 Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu
 275 280 285
 Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu
 290 295 300
 Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu
 305 310 315 320
 His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu
 325 330 335
 Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met

340					345					350					
Lys	Asn	Leu	Ser	His	Ile	Tyr	Phe	Lys	Asn	Phe	Arg	Tyr	Cys	Ser	Tyr
	355						360					365			
Ala	Pro	His	Val	Arg	Ile	Cys	Met	Pro	Leu	Thr	Asp	Gly	Ile	Ser	Ser
	370					375					380				
Phe	Glu	Asp	Leu	Leu	Ala	Asn	Asn	Ile	Leu	Arg	Ile	Phe	Val	Trp	Val
385					390					395					400
Ile	Ala	Phe	Ile	Thr	Cys	Phe	Gly	Asn	Leu	Phe	Val	Ile	Gly	Met	Arg
			405					410						415	
Ser	Phe	Ile	Lys	Ala	Glu	Asn	Thr	Thr	His	Ala	Met	Ser	Ile	Lys	Ile
			420					425					430		
Leu	Cys	Cys	Ala	Asp	Cys	Leu	Met	Gly	Val	Tyr	Leu	Phe	Phe	Val	Gly
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Ile	Phe	Asp	Ile	Lys	Tyr	Arg	Gly	Gln	Tyr	Gln	Lys	Tyr	Ala	Leu	Leu
	450					455					460				
Trp	Met	Glu	Ser	Val	Gln	Cys	Arg	Leu	Met	Gly	Phe	Leu	Ala	Met	Leu
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Ser	Thr	Glu	Val	Ser	Val	Leu	Leu	Leu	Thr	Tyr	Leu	Thr	Leu	Glu	Lys
			485						490					495	
Phe	Leu	Val	Ile	Val	Phe	Pro	Phe	Ser	Asn	Ile	Arg	Pro	Gly	Lys	Arg
		500						505					510		
Gln	Thr	Ser	Val	Ile	Leu	Ile	Cys	Ile	Trp	Met	Ala	Gly	Phe	Leu	Ile
		515					520					525			
Ala	Val	Ile	Pro	Phe	Trp	Asn	Lys	Asp	Tyr	Phe	Gly	Asn	Phe	Tyr	Gly
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Lys	Asn	Gly	Val	Cys	Phe	Pro	Leu	Tyr	Tyr	Asp	Gln	Thr	Glu	Asp	Ile
545						550					555				560
Gly	Ser	Lys	Gly	Tyr	Ser	Leu	Gly	Ile	Phe	Leu	Gly	Val	Asn	Leu	Leu
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Ala	Phe	Leu	Ile	Ile	Val	Phe	Ser	Tyr	Ile	Thr	Met	Phe	Cys	Ser	Ile
		580						585					590		
Gln	Lys	Thr	Ala	Leu	Gln	Thr	Thr	Glu	Val	Arg	Asn	Cys	Phe	Gly	Arg
		595					600					605			
Glu	Val	Ala	Val	Ala	Asn	Arg	Phe	Phe	Phe	Ile	Val	Phe	Ser	Asp	Ala
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Ile	Cys	Trp	Ile	Pro	Val	Phe	Val	Val	Lys	Ile	Leu	Ser	Leu	Phe	Arg
625						630					635				640
Val	Glu	Ile	Pro	Asp	Thr	Met	Thr	Ser	Trp	Ile	Val	Ile	Phe	Phe	Leu
			645						650					655	
Pro	Val	Asn	Ser	Ala	Leu	Asn	Pro	Ile	Leu	Tyr	Thr	Leu	Thr	Thr	Asn
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Phe Phe Lys Asp Lys Leu Lys Gln Leu Leu His Lys His Gln Arg Lys
 675 680 685

Ser Ile Phe Lys Ile Lys Lys Lys Ser Leu Ser Thr Ser Ile Val Trp
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Leu Gly Asp Ser Ile Met Lys Pro Val Ser
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Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60

Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80

Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95

Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110

Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125

Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140

Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys
 145 150 155 160

Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr
 165 170 175

Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu
 180 185 190

Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr
 195 200 205

Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn
 210 215 220

Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr
 225 230 235 240
 Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr
 245 250 255
 Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln
 260 265 270
 Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln
 275 280 285
 Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu
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 Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser
 305 310 315 320
 His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val
 325 330 335
 Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu
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 Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile
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 Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys
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 Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala
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 Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser
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 Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val
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 Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly
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 Tyr Ser Leu Gly Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile
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Ile Val Phe Ser Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala
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 565 570 575
 Ala Asn Arg Phe Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile
 580 585 590
 Pro Val Phe Val Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro
 595 600 605
 Asp Thr Met Thr Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser
 610 615 620
 Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp
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 Lys Leu Lys Gln Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys
 645 650 655
 Ile Lys Lys Lys Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser
 660 665 670
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 Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys
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 ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag 96
 Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys
 20 25 30
 gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt 144
 Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser
 35 40 45
 gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg 192
 Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60
 gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac 240
 Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80

tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg	288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val	
85 90 95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa	336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa	384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys	
115 120 125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca	432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala	
130 135 140	
ttt ttt gga tta tgt aat ctg caa ata tta tat ctc aac cac aac tgc	480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys	
145 150 155 160	
atc aca acc ctc aga cct gga ata ttc aaa gac tta cat cag cta act	528
Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr	
165 170 175	
tgg cta att cta gat gac aat cca ata acc aga att tca cag cgc ttg	576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu	
180 185 190	
ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac	624
Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr	
195 200 205	
tta gaa gct ctt ccc aag cag atg tgt gcc caa atg cct caa ctc aac	672
Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn	
210 215 220	
tgg gtg gat ttg gaa ggc aat aga ata aag tat ctc aca aat tct acg	720
Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr	
225 230 235 240	
ttt ctg tcg tgc gat tcg ctc aca gtg ctg gat ctg tct agc aat acg	768
Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr	
245 250 255	
ata acg gag cta tca cct cac ctt ttt aaa gac ttg aag ctt cta caa	816
Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln	
260 265 270	
aag ctg aac ctg tca tcc aat cct ctt atg tat ctt cac aag aac cag	864
Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln	
275 280 285	
ttt gaa agt ctt aaa caa ctt cag tct cta gac ctg gaa agg ata gag	912
Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu	
290 295 300	
att cca aat ata aac aca cga atg ttt caa ccc atg aag aat ctt tct	960
Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser	
305 310 315 320	
cac att tat ttc aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc	1008

His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val
 325 330 335
 cga ata tgt atg ccc ttg acg gac ggc att tct tca ttt gag gac ctc 1056
 Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu
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 ttg gct aac aat atc ctc aga 1077
 Leu Ala Asn Asn Ile Leu Arg
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 35 40 45
 Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60
 Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80
 Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95
 Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110
 Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125
 Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140
 Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys
 145 150 155 160
 Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr
 165 170 175
 Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu
 180 185 190
 Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr
 195 200 205
 Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn
 210 215 220
 Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr

225 230 235 240
 Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr
 245 250 255
 Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln
 260 265 270
 Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln
 275 280 285
 Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu
 290 295 300
 Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser
 305 310 315 320
 His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val
 325 330 335
 Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu
 340 345 350
 Leu Ala Asn Asn Ile Leu Arg
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 aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat 96
 Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp
 20 25 30
 ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga 144
 Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45
 tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac 192
 Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His
 50 55 60
 tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt 240
 Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys
 65 70 75 80

ggt gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta att cta	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu	
180 185 190	
gat gac aat cca ata acc aga att tca cag cgc ttg ttt acg gga tta	624
Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu	
195 200 205	
aat tcc ttg ttt ttc ctg tct atg gtt aat aac tac tta gaa gct ctt	672
Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu	
210 215 220	
ccc aag cag atg tgt gcc caa atg cct caa ctc aac tgg gtg gat ttg	720
Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu	
225 230 235 240	
gaa ggc aat aga ata aag tat ctc aca aat tct acg ttt ctg tcg tgc	768
Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys	
245 250 255	
gat tcg ctc aca gtg ctg gat ctg tct agc aat acg ata acg gag cta	816
Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu	
260 265 270	
tca cct cac ctt ttt aaa gac ttg aag ctt cta caa aag cta gac ctg	864
Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu	
275 280 285	
gaa agg ata gag att cca aat ata aac aca cga atg ttt caa ccc atg	912
Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met	
290 295 300	
aag aat ctt tct cac att tat ttc aaa aac ttt cga tac tgc tcc tat	960
Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr	
305 310 315 320	
gct ccc cat gtc cga ata tgt atg ccc ttg acg gac ggc att tct tca	1008

Ala	Pro	His	Val	Arg	Ile	Cys	Met	Pro	Leu	Thr	Asp	Gly	Ile	Ser	Ser		
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ttt	gag	gac	ctc	ttg	gct	aac	aat	atc	ctc	aga	ata	ttt	gtc	tgg	gtt	1056	
Phe	Glu	Asp	Leu	Leu	Ala	Asn	Asn	Ile	Leu	Arg	Ile	Phe	Val	Trp	Val		
			340					345					350				
ata	gct	ttc	att	acc	tgc	ttt	gga	aat	ctt	ttt	gtc	att	ggc	atg	aga	1104	
Ile	Ala	Phe	Ile	Thr	Cys	Phe	Gly	Asn	Leu	Phe	Val	Ile	Gly	Met	Arg		
			355				360					365					
tct	ttc	att	aaa	gct	gaa	aat	aca	act	cac	gct	atg	tcc	atc	aaa	atc	1152	
Ser	Phe	Ile	Lys	Ala	Glu	Asn	Thr	Thr	His	Ala	Met	Ser	Ile	Lys	Ile		
	370					375					380						
ctt	tgt	tgt	gct	gat	tgc	ctg	atg	ggg	gtt	tac	ttg	ttc	ttt	gtt	ggc	1200	
Leu	Cys	Cys	Ala	Asp	Cys	Leu	Met	Gly	Val	Tyr	Leu	Phe	Phe	Val	Gly		
385					390					395				400			
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Ile	Phe	Asp	Ile	Lys	Tyr	Arg	Gly	Gln	Tyr	Gln	Lys	Tyr	Ala	Leu	Leu		
				405				410						415			
tgg	atg	gag	agc	gtg	cag	tgc	cgc	ctc	atg	ggg	ttc	ctg	gcc	atg	ctg	1296	
Trp	Met	Glu	Ser	Val	Gln	Cys	Arg	Leu	Met	Gly	Phe	Leu	Ala	Met	Leu		
			420					425					430				
tcc	acc	gaa	gtc	tct	gtt	ctg	cta	ctg	acc	tac	ttg	act	ttg	gag	aag	1344	
Ser	Thr	Glu	Val	Ser	Val	Leu	Leu	Leu	Thr	Tyr	Leu	Thr	Leu	Glu	Lys		
			435				440					445					
ttc	ctg	gtc	att	gtc	ttc	ccc	ttc	agt	aac	att	cga	cct	gga	aaa	cgg	1392	
Phe	Leu	Val	Ile	Val	Phe	Pro	Phe	Ser	Asn	Ile	Arg	Pro	Gly	Lys	Arg		
	450					455					460						
cag	acc	tca	gtc	atc	ctc	att	tgc	atc	tgg	atg	gcg	gga	ttt	tta	ata	1440	
Gln	Thr	Ser	Val	Ile	Leu	Ile	Cys	Ile	Trp	Met	Ala	Gly	Phe	Leu	Ile		
465					470				475						480		
gct	gta	att	cca	ttt	tgg	aat	aag	gat	tat	ttt	gga	aac	ttt	tat	ggg	1488	
Ala	Val	Ile	Pro	Phe	Trp	Asn	Lys	Asp	Tyr	Phe	Gly	Asn	Phe	Tyr	Gly		
				485				490						495			
aaa	aat	gga	gta	tgt	ttc	cca	ctt	tat	tat	gac	caa	aca	gaa	gat	att	1536	
Lys	Asn	Gly	Val	Cys	Phe	Pro	Leu	Tyr	Tyr	Asp	Gln	Thr	Glu	Asp	Ile		
			500					505					510				
gga	agc	aaa	ggg	tat	tct	ctt	gga	att	ttc	cta	ggg	gtg	aac	ttg	ctg	1584	
Gly	Ser	Lys	Gly	Tyr	Ser	Leu	Gly	Ile	Phe	Leu	Gly	Val	Asn	Leu	Leu		
		515					520					525					
gct	ttt	ctc	atc	att	gtg	ttt	tcc	tat	att	act	atg	ttc	tgt	tcc	att	1632	
Ala	Phe	Leu	Ile	Ile	Val	Phe	Ser	Tyr	Ile	Thr	Met	Phe	Cys	Ser	Ile		
		530				535					540						
caa	aaa	acc	gcc	ttg	cag	acc	aca	gaa	gta	agg	aat	tgt	ttt	gga	aga	1680	
Gln	Lys	Thr	Ala	Leu	Gln	Thr	Thr	Glu	Val	Arg	Asn	Cys	Phe	Gly	Arg		
545					550					555					560		
gag	gtg	gct	gtt	gca	aat	cgt	ttc	ttt	ttt	ata	gtg	ttc	tct	gat	gcc	1728	
Glu	Val	Ala	Val	Ala	Asn	Arg	Phe	Phe	Phe	Ile	Val	Phe	Ser	Asp	Ala		

565										570					575					
atc tgc tgg att cct gta ttt gta gtt aaa atc ctt tcc ctc ttc cgg	1776																			
Ile Cys Trp Ile Pro Val Phe Val Val Lys Ile Leu Ser Leu Phe Arg																				
580 585 590																				
gtg gaa ata cca gac aca atg act tcc tgg ata gtg att ttt ttc ctt	1824																			
Val Glu Ile Pro Asp Thr Met Thr Ser Trp Ile Val Ile Phe Phe Leu																				
595 600 605																				
cca gtt aac agt gct ttg aat cca atc ctc tat act ctc aca acc aac	1872																			
Pro Val Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Asn																				
610 615 620																				
ttt ttt aag gac aag ttg aaa cag ctg ctg cac aaa cat cag agg aaa	1920																			
Phe Phe Lys Asp Lys Leu Lys Gln Leu Leu His Lys His Gln Arg Lys																				
625 630 635 640																				
tca att ttc aaa att aaa aaa aaa agt tta tct aca tcc att gtg tgg	1968																			
Ser Ile Phe Lys Ile Lys Lys Lys Ser Leu Ser Thr Ser Ile Val Trp																				
645 650 655																				
ata gag gac tcc tct tcc ctg aaa ctt ggg gtt ttg aac aaa ata aca	2016																			
Ile Glu Asp Ser Ser Ser Leu Lys Leu Gly Val Leu Asn Lys Ile Thr																				
660 665 670																				
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 Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45
 Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His
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 Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys
 65 70 75 80
 Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn
 85 90 95
 Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro
 100 105 110
 Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp
 115 120 125

Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu
 130 135 140
 Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr
 145 150 155 160
 Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile
 165 170 175
 Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu
 180 185 190
 Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu
 195 200 205
 Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu
 210 215 220
 Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu
 225 230 235 240
 Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys
 245 250 255
 Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu
 260 265 270
 Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu
 275 280 285
 Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met
 290 295 300
 Lys Asn Leu Ser His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr
 305 310 315 320
 Ala Pro His Val Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser
 325 330 335
 Phe Glu Asp Leu Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val
 340 345 350
 Ile Ala Phe Ile Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg
 355 360 365
 Ser Phe Ile Lys Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile
 370 375 380
 Leu Cys Cys Ala Asp Cys Leu Met Gly Val Tyr Leu Phe Phe Val Gly
 385 390 395 400
 Ile Phe Asp Ile Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu
 405 410 415
 Trp Met Glu Ser Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu
 420 425 430
 Ser Thr Glu Val Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu Glu Lys
 435 440 445
 Phe Leu Val Ile Val Phe Pro Phe Ser Asn Ile Arg Pro Gly Lys Arg

450 455 460
 Gln Thr Ser Val Ile Leu Ile Cys Ile Trp Met Ala Gly Phe Leu Ile
 465 470 475 480
 Ala Val Ile Pro Phe Trp Asn Lys Asp Tyr Phe Gly Asn Phe Tyr Gly
 485 490 495
 Lys Asn Gly Val Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu Asp Ile
 500 505 510
 Gly Ser Lys Gly Tyr Ser Leu Gly Ile Phe Leu Gly Val Asn Leu Leu
 515 520 525
 Ala Phe Leu Ile Ile Val Phe Ser Tyr Ile Thr Met Phe Cys Ser Ile
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 Gln Lys Thr Ala Leu Gln Thr Thr Glu Val Arg Asn Cys Phe Gly Arg
 545 550 555 560
 Glu Val Ala Val Ala Asn Arg Phe Phe Phe Ile Val Phe Ser Asp Ala
 565 570 575
 Ile Cys Trp Ile Pro Val Phe Val Val Lys Ile Leu Ser Leu Phe Arg
 580 585 590
 Val Glu Ile Pro Asp Thr Met Thr Ser Trp Ile Val Ile Phe Phe Leu
 595 600 605
 Pro Val Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Asn
 610 615 620
 Phe Phe Lys Asp Lys Leu Lys Gln Leu Leu His Lys His Gln Arg Lys
 625 630 635 640
 Ser Ile Phe Lys Ile Lys Lys Lys Ser Leu Ser Thr Ser Ile Val Trp
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 Leu Gly Asp Ser Ile Met Lys Pro Val Ser
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<211> 646

<212> PRT

<213> Homo sapiens

<400> 13

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 35 40 45

Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val

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Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp 65 70 75 80		
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val 85 90 95		
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys 100 105 110		
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys 115 120 125		
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala 130 135 140		
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu Asp Asp Asn Pro 145 150 155 160		
Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe 165 170 175		
Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met 180 185 190		
Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg 195 200 205		
Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr 210 215 220		
Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu 225 230 235 240		
Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu Glu Arg Ile Glu 245 250 255		
Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser 260 265 270		
His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val 275 280 285		
Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu 290 295 300		
Leu Ala Asn Asn Ile Leu Arg Ile Phe Val Trp Val Ile Ala Phe Ile 305 310 315 320		
Thr Cys Phe Gly Asn Leu Phe Val Ile Gly Met Arg Ser Phe Ile Lys 325 330 335		
Ala Glu Asn Thr Thr His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala 340 345 350		
Asp Cys Leu Met Gly Val Tyr Leu Phe Phe Val Gly Ile Phe Asp Ile 355 360 365		
Lys Tyr Arg Gly Gln Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser 370 375 380		

Val Gln Cys Arg Leu Met Gly Phe Leu Ala Met Leu Ser Thr Glu Val
 385 390 395 400
 Ser Val Leu Leu Leu Thr Tyr Leu Thr Leu Glu Lys Phe Leu Val Ile
 405 410 415
 Val Phe Pro Phe Ser Asn Ile Arg Pro Gly Lys Arg Gln Thr Ser Val
 420 425 430
 Ile Leu Ile Cys Ile Trp Met Ala Gly Phe Leu Ile Ala Val Ile Pro
 435 440 445
 Phe Trp Asn Lys Asp Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val
 450 455 460
 Cys Phe Pro Leu Tyr Tyr Asp Gln Thr Glu Asp Ile Gly Ser Lys Gly
 465 470 475 480
 Tyr Ser Leu Gly Ile Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Ile
 485 490 495
 Ile Val Phe Ser Tyr Ile Thr Met Phe Cys Ser Ile Gln Lys Thr Ala
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 Leu Gln Thr Thr Glu Val Arg Asn Cys Phe Gly Arg Glu Val Ala Val
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 Ala Asn Arg Phe Phe Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile
 530 535 540
 Pro Val Phe Val Val Lys Ile Leu Ser Leu Phe Arg Val Glu Ile Pro
 545 550 555 560
 Asp Thr Met Thr Ser Trp Ile Val Ile Phe Phe Leu Pro Val Asn Ser
 565 570 575
 Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Asn Phe Phe Lys Asp
 580 585 590
 Lys Leu Lys Gln Leu Leu His Lys His Gln Arg Lys Ser Ile Phe Lys
 595 600 605
 Ile Lys Lys Lys Ser Leu Ser Thr Ser Ile Val Trp Ile Glu Asp Ser
 610 615 620
 Ser Ser Leu Lys Leu Gly Val Leu Asn Lys Ile Thr Leu Gly Asp Ser
 625 630 635 640
 Ile Met Lys Pro Val Ser
 645

<210> 14
 <211> 933
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(933)

<400> 14

caa ggt agc atg atc act cct tca tgc caa aaa gga tat ttt ccc tgt	48
Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys	
1 5 10 15	
ggg aat ctt acc aag tgc tta ccc cga gct ttt cac tgt gat ggc aag	96
Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys	
20 25 30	
gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt ggt gac act agt	144
Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser	
35 40 45	
gga tgg gcg acc ata ttt ggc aca gtg cat gga aat gct aac agc gtg	192
Gly Trp Ala Thr Ile Phe Thr Val His Gly Asn Ala Asn Ser Val	
50 55 60	
gcc tta aca cag gag tgc ttt cta aaa cag tat cca caa tgc tgt gac	240
Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp	
65 70 75 80	
tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac tta aag tct gtg	288
Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val	
85 90 95	
ccg atg att tct aac aat gtg aca tta ctg tct ctt aag aaa aac aaa	336
Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys	
100 105 110	
atc cac agt ctt cca gat aaa gtt ttc atc aaa tac aca aaa ctt aaa	384
Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys	
115 120 125	
aag ata ttt ctt cag cat aat tgc att aga cac ata tcc agg aaa gca	432
Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala	
130 135 140	
ttt ttt gga tta tgt aat ctg caa ata tta att cta gat gac aat cca	480
Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu Asp Asp Asn Pro	
145 150 155 160	
ata acc aga att tca cag cgc ttg ttt acg gga tta aat tcc ttg ttt	528
Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe	
165 170 175	
ttc ctg tct atg gtt aat aac tac tta gaa gct ctt ccc aag cag atg	576
Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met	
180 185 190	
tgt gcc caa atg cct caa ctc aac tgg gtg gat ttg gaa ggc aat aga	624
Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg	
195 200 205	
ata aag tat ctc aca aat tct acg ttt ctg tcg tgc gat tcg ctc aca	672
Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr	
210 215 220	
gtg ctg gat ctg tct agc aat acg ata acg gag cta tca cct cac ctt	720
Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu	
225 230 235 240	

ttt aaa gac ttg aag ctt cta caa aag cta gac ctg gaa agg ata gag 768
 Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu Glu Arg Ile Glu
 245 250 255
 att cca aat ata aac aca cga atg ttt caa ccc atg aag aat ctt tct 816
 Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser
 260 265 270
 cac att tat ttc aaa aac ttt cga tac tgc tcc tat gct ccc cat gtc 864
 His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val
 275 280 285
 cga ata tgt atg ccc ttg acg gac ggc att tct tca ttt gag gac ctc 912
 Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu
 290 295 300
 ttg gct aac aat atc ctc aga 933
 Leu Ala Asn Asn Ile Leu Arg
 305 310

<210> 15
 <211> 311
 <212> PRT
 <213> Homo sapiens

<400> 15
 Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys
 1 5 10 15
 Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys
 20 25 30
 Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser
 35 40 45
 Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60
 Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80
 Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95
 Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110
 Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125
 Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140
 Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Ile Leu Asp Asp Asn Pro
 145 150 155 160
 Ile Thr Arg Ile Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe
 165 170 175

Phe Leu Ser Met Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met
 180 185 190
 Cys Ala Gln Met Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg
 195 200 205
 Ile Lys Tyr Leu Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr
 210 215 220
 Val Leu Asp Leu Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu
 225 230 235 240
 Phe Lys Asp Leu Lys Leu Leu Gln Lys Leu Asp Leu Glu Arg Ile Glu
 245 250 255
 Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser
 260 265 270
 His Ile Tyr Phe Lys Asn Phe Arg Tyr Cys Ser Tyr Ala Pro His Val
 275 280 285
 Arg Ile Cys Met Pro Leu Thr Asp Gly Ile Ser Ser Phe Glu Asp Leu
 290 295 300
 Leu Ala Asn Asn Ile Leu Arg
 305 310

<210> 16
 <211> 1101
 <212> DNA
 <213> Homo sapiens

<220>
 <221> CDS
 <222> (1)..(1098)

<220>
 <221> sig_peptide
 <222> (1)..(108)

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 Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile
 1 5 10 15
 aca atg ttc ttt cta ctt cat ttc atc gtt ctg atc aat gtc aaa gat 96
 Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp
 20 25 30
 ttt gca ctg act caa ggt agc atg atc act cct tca tgc caa aaa gga 144
 Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45
 tat ttt ccc tgt ggg aat ctt acc aag tgc tta ccc cga gct ttt cac 192
 Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His
 50 55 60
 tgt gat ggc aag gat gac tgt ggg aac ggg gcg gac gaa gag aac tgt 240
 Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys
 65 70 75 80

ggt gac act agt gga tgg gcg acc ata ttt ggc aca gtg cat gga aat	288
Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn	
85 90 95	
gct aac agc gtg gcc tta aca cag gag tgc ttt cta aaa cag tat cca	336
Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro	
100 105 110	
caa tgc tgt gac tgc aaa gaa act gaa ttg gaa tgt gta aat ggt gac	384
Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp	
115 120 125	
tta aag tct gtg ccg atg att tct aac aat gtg aca tta ctg tct ctt	432
Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu	
130 135 140	
aag aaa aac aaa atc cac agt ctt cca gat aaa gtt ttc atc aaa tac	480
Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr	
145 150 155 160	
aca aaa ctt aaa aag ata ttt ctt cag cat aat tgc att aga cac ata	528
Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile	
165 170 175	
tcc agg aaa gca ttt ttt gga tta tgt aat ctg caa ata tta tat ctc	576
Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu	
180 185 190	
aac cac aac tgc atc aca acc ctc aga cct gga ata ttc aaa gac tta	624
Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu	
195 200 205	
cat cag cta act tgg cta att cta gat gac aat cca ata acc aga att	672
His Gln Leu Thr Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile	
210 215 220	
tca cag cgc ttg ttt acg gga tta aat tcc ttg ttt ttc ctg tct atg	720
Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met	
225 230 235 240	
gtt aat aac tac tta gaa gct ctt ccc aag cag atg tgt gcc caa atg	768
Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met	
245 250 255	
cct caa ctc aac tgg gtg gat ttg gaa ggc aat aga ata aag tat ctc	816
Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu	
260 265 270	
aca aat tct acg ttt ctg tgc tgc gat tgc ctc aca gtg ctg gat ctg	864
Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu	
275 280 285	
tct agc aat acg ata acg gag cta tca cct cac ctt ttt aaa gac ttg	912
Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu	
290 295 300	
aag ctt cta caa aag ctg aac ctg tca tcc aat cct ctt atg tat ctt	960
Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu	
305 310 315 320	

cac aag aac cag ttt gaa agt ctt aaa caa ctt cag tct cta gac ctg 1008
 His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu
 325 330 335

gaa agg ata gag att cca aat ata aac aca cga atg ttt caa ccc atg 1056
 Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met
 340 345 350

aag aat ctt tct cac ata gtt caa tat tat gat gtg ccg aca tga 1101
 Lys Asn Leu Ser His Ile Val Gln Tyr Tyr Asp Val Pro Thr
 355 360 365

<210> 17

<211> 366

<212> PRT

<213> Homo sapiens

<400> 17

Met Ile Val Phe Leu Val Phe Lys His Leu Phe Ser Leu Arg Leu Ile
 1 5 10 15

Thr Met Phe Phe Leu Leu His Phe Ile Val Leu Ile Asn Val Lys Asp
 20 25 30

Phe Ala Leu Thr Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly
 35 40 45

Tyr Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His
 50 55 60

Cys Asp Gly Lys Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys
 65 70 75 80

Gly Asp Thr Ser Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn
 85 90 95

Ala Asn Ser Val Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro
 100 105 110

Gln Cys Cys Asp Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp
 115 120 125

Leu Lys Ser Val Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu
 130 135 140

Lys Lys Asn Lys Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr
 145 150 155 160

Thr Lys Leu Lys Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile
 165 170 175

Ser Arg Lys Ala Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu
 180 185 190

Asn His Asn Cys Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu
 195 200 205

His Gln Leu Thr Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile
 210 215 220

Ser Gln Arg Leu Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met
 225 230 235 240
 Val Asn Asn Tyr Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met
 245 250 255
 Pro Gln Leu Asn Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu
 260 265 270
 Thr Asn Ser Thr Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu
 275 280 285
 Ser Ser Asn Thr Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu
 290 295 300
 Lys Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu
 305 310 315 320
 His Lys Asn Gln Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu
 325 330 335
 Glu Arg Ile Glu Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met
 340 345 350
 Lys Asn Leu Ser His Ile Val Gln Tyr Tyr Asp Val Pro Thr
 355 360 365

<210> 18
 <211> 330
 <212> PRT
 <213> Homo sapiens

<400> 18
 Gln Gly Ser Met Ile Thr Pro Ser Cys Gln Lys Gly Tyr Phe Pro Cys
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 Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Lys
 20 25 30
 Asp Asp Cys Gly Asn Gly Ala Asp Glu Glu Asn Cys Gly Asp Thr Ser
 35 40 45
 Gly Trp Ala Thr Ile Phe Gly Thr Val His Gly Asn Ala Asn Ser Val
 50 55 60
 Ala Leu Thr Gln Glu Cys Phe Leu Lys Gln Tyr Pro Gln Cys Cys Asp
 65 70 75 80
 Cys Lys Glu Thr Glu Leu Glu Cys Val Asn Gly Asp Leu Lys Ser Val
 85 90 95
 Pro Met Ile Ser Asn Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110
 Ile His Ser Leu Pro Asp Lys Val Phe Ile Lys Tyr Thr Lys Leu Lys
 115 120 125
 Lys Ile Phe Leu Gln His Asn Cys Ile Arg His Ile Ser Arg Lys Ala
 130 135 140

Phe Phe Gly Leu Cys Asn Leu Gln Ile Leu Tyr Leu Asn His Asn Cys
 145 150 155 160
 Ile Thr Thr Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Thr
 165 170 175
 Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Arg Leu
 180 185 190
 Phe Thr Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Asn Asn Tyr
 195 200 205
 Leu Glu Ala Leu Pro Lys Gln Met Cys Ala Gln Met Pro Gln Leu Asn
 210 215 220
 Trp Val Asp Leu Glu Gly Asn Arg Ile Lys Tyr Leu Thr Asn Ser Thr
 225 230 235 240
 Phe Leu Ser Cys Asp Ser Leu Thr Val Leu Asp Leu Ser Ser Asn Thr
 245 250 255
 Ile Thr Glu Leu Ser Pro His Leu Phe Lys Asp Leu Lys Leu Leu Gln
 260 265 270
 Lys Leu Asn Leu Ser Ser Asn Pro Leu Met Tyr Leu His Lys Asn Gln
 275 280 285
 Phe Glu Ser Leu Lys Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu
 290 295 300
 Ile Pro Asn Ile Asn Thr Arg Met Phe Gln Pro Met Lys Asn Leu Ser
 305 310 315 320
 His Ile Val Gln Tyr Tyr Asp Val Pro Thr
 325 330

<210> 19
 <211> 2214
 <212> DNA
 <213> Mus musculus

<220>
 <221> CDS
 <222> (1)..(2211)

<220>
 <221> sig_peptide
 <222> (1)..(57)

<400> 19
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 Met Trp Leu Leu Leu His Val Ile Leu Leu Thr Glu Val Lys Asp Phe
 1 5 10 15
 gca ctg gct gac agc agt atg gtg gct cct ctg tgc ccc aaa ggg tat 96
 Ala Leu Ala Asp Ser Ser Met Val Ala Pro Leu Cys Pro Lys Gly Tyr
 20 25 30
 ttt ccc tgt ggg aat ctc acc aaa tgc ttg ccc cga gcc ttt cac tgc 144
 Phe Pro Cys Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys

35					40					45									
gat	ggt	gtg	gat	gat	tgc	ggg	aat	ggt	gcc	gac	gag	gac	aac	tgt	ggt	192			
Asp	Gly	Val	Asp	Asp	Cys	Gly	Asn	Gly	Ala	Asp	Glu	Asp	Asn	Cys	Gly				
	50					55					60								
gac	act	agt	gga	tgg	aca	acc	ata	ttt	ggc	aca	gtc	cat	ggg	aat	gtc	240			
Asp	Thr	Ser	Gly	Trp	Thr	Thr	Ile	Phe	Gly	Thr	Val	His	Gly	Asn	Val				
	65				70					75					80				
aat	aaa	gtg	aca	ttg	aca	cag	gag	tgc	ttt	ctc	agc	cag	tat	cca	cag	288			
Asn	Lys	Val	Thr	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Ser	Gln	Tyr	Pro	Gln				
				85					90					95					
cac	tgt	tac	tgc	aga	gaa	aat	gaa	ctg	gaa	tgt	gta	aag	gct	gac	tta	336			
His	Cys	Tyr	Cys	Arg	Glu	Asn	Glu	Leu	Glu	Cys	Val	Lys	Ala	Asp	Leu				
			100					105					110						
aaa	gct	gtg	cca	aag	gtt	tcc	agc	aac	gta	aca	tta	cta	tct	ctt	aag	384			
Lys	Ala	Val	Pro	Lys	Val	Ser	Ser	Asn	Val	Thr	Leu	Leu	Ser	Leu	Lys				
		115					120					125							
aaa	aac	aaa	atc	cac	aga	ctt	cca	gtc	aag	gtc	ttc	agc	aga	tac	aca	432			
Lys	Asn	Lys	Ile	His	Arg	Leu	Pro	Val	Lys	Val	Phe	Ser	Arg	Tyr	Thr				
	130					135					140								
gaa	ctc	aga	aag	ata	tac	ctt	cag	cac	aac	tgc	atc	aca	cac	atc	tcc	480			
Glu	Leu	Arg	Lys	Ile	Tyr	Leu	Gln	His	Asn	Cys	Ile	Thr	His	Ile	Ser				
	145				150					155					160				
agg	aga	gca	ttc	ctt	gga	tta	cat	aat	cta	caa	ata	ctg	tat	ctc	agc	528			
Arg	Arg	Ala	Phe	Leu	Gly	Leu	His	Asn	Leu	Gln	Ile	Leu	Tyr	Leu	Ser				
				165					170					175					
cat	aac	tgc	att	acc	tct	ctc	agg	cct	ggg	ata	ttc	aaa	gac	ttg	cat	576			
His	Asn	Cys	Ile	Thr	Ser	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu	His				
			180					185					190						
cag	ctt	gct	tgg	cta	att	tta	gat	gac	aac	ccg	atc	acc	aga	atc	tca	624			
Gln	Leu	Ala	Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile	Ser				
		195					200					205							
cag	aag	tcc	ttt	atg	ggg	tta	aac	tcc	ttg	ttt	ttc	ttg	tcc	atg	gtg	672			
Gln	Lys	Ser	Phe	Met	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met	Val				
	210					215					220								
ggt	aac	cgg	ctc	gag	gcc	ctt	cct	gaa	aca	ttg	tgt	gct	cag	atg	cct	720			
Gly	Asn	Arg	Leu	Glu	Ala	Leu	Pro	Glu	Thr	Leu	Cys	Ala	Gln	Met	Pro				
	225				230					235					240				
caa	ctc	aac	tgg	gtg	gat	ctg	gca	aac	aat	gga	ata	aag	tac	ata	acg	768			
Gln	Leu	Asn	Trp	Val	Asp	Leu	Ala	Asn	Asn	Gly	Ile	Lys	Tyr	Ile	Thr				
				245					250					255					
aac	tcc	acc	ttc	cta	acg	tgc	gac	tcg	ctc	acg	gtt	ctg	ttt	ctg	cct	816			
Asn	Ser	Thr	Phe	Leu	Thr	Cys	Asp	Ser	Leu	Thr	Val	Leu	Phe	Leu	Pro				
			260					265				270							
aga	aat	caa	att	ggt	ttt	gtt	cca	gag	aag	aca	ttt	tct	tca	tta	aaa	864			
Arg	Asn	Gln	Ile	Gly	Phe	Val	Pro	Glu	Lys	Thr	Phe	Ser	Ser	Leu	Lys				
		275					280					285							

aat tta gga gaa ctg gac ctg tct agc aat atg ata aca aaa ctc cca	912
Asn Leu Gly Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro	
290 295 300	
gtc cac ctt ttc agc gac ctt cat ctt ctc cag aag ctg aac ctg tca	960
Val His Leu Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser	
305 310 315 320	
tcc aac cct ctt ctg tat gtc cac aag aac cag ttt gga agt ctc aaa	1008
Ser Asn Pro Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys	
325 330 335	
caa ctt cag tct cta gac ctg gaa agg ata gag att cca aac ata agc	1056
Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Ser	
340 345 350	
aca gga atg ttc cag cca atg aag aac ctt tct cac att tat ttg aaa	1104
Thr Gly Met Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Leu Lys	
355 360 365	
acc ttt cga tac tgc tcc tat gtc ccc cat gtc cga atc tgt atg ccg	1152
Thr Phe Arg Tyr Cys Ser Tyr Val Pro His Val Arg Ile Cys Met Pro	
370 375 380	
tcg act gat ggt att tct tcg tct gag gac ctc ttg gct aac ggt atc	1200
Ser Thr Asp Gly Ile Ser Ser Ser Glu Asp Leu Leu Ala Asn Gly Ile	
385 390 395 400	
ctc aga gtg tct gtc tgg gtt ata gct ttc att acc tgc gtt ggg aat	1248
Leu Arg Val Ser Val Trp Val Ile Ala Phe Ile Thr Cys Val Gly Asn	
405 410 415	
ttc ctt gtc ata gcc gtg aga tct ctc att aag gct gag aat aca act	1296
Phe Leu Val Ile Ala Val Arg Ser Leu Ile Lys Ala Glu Asn Thr Thr	
420 425 430	
cac gct atg tcc atc aaa atc ctt tgt tgt gcc gat tgc ctg atg ggg	1344
His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met Gly	
435 440 445	
gtg tac ctg ttc tcc gtg ggc gtc ttt gac atc aag tac cga ggg cag	1392
Val Tyr Leu Phe Ser Val Gly Val Phe Asp Ile Lys Tyr Arg Gly Gln	
450 455 460	
tat cag aag tat gcg ctg ctg tgg atg gag agt gtg ccc tgc cgc ctg	1440
Tyr Gln Lys Tyr Ala Leu Leu Trp Met Glu Ser Val Pro Cys Arg Leu	
465 470 475 480	
ctg ggc ttc ctg gcc acg ctg tcc aca gag gtc tcg gtg ctg ctg ctg	1488
Leu Gly Phe Leu Ala Thr Leu Ser Thr Glu Val Ser Val Leu Leu Leu	
485 490 495	
aca ttc ctg acg ctg gag aag ttc ctt gtc ata gta ttc cct ttc agc	1536
Thr Phe Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe Ser	
500 505 510	
aac ctg cgc ctg ggc aag cgc cag act gct gtg gcc ctc gcc agc atc	1584
Asn Leu Arg Leu Gly Lys Arg Gln Thr Ala Val Ala Leu Ala Ser Ile	
515 520 525	

tgg gtg gtg gga ttt ctc ata gcg gcc gtt ccg ttc acc aga gag gat	1632
Trp Val Val Gly Phe Leu Ile Ala Ala Val Pro Phe Thr Arg Glu Asp	
530 535 540	
tat ttc ggc aac ttt tat ggg aaa aat gga gtc tgc ttc cca ctt cat	1680
Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu His	
545 550 555 560	
tat gac caa gca gaa gat ttt gga agt aga ggg tac tcc ctt ggg att	1728
Tyr Asp Gln Ala Glu Asp Phe Gly Ser Arg Gly Tyr Ser Leu Gly Ile	
565 570 575	
ttc cta ggt gtg aac ttg ctg gct ttc ctc gtc atc gtg att tcc tat	1776
Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Val Ile Val Ile Ser Tyr	
580 585 590	
gtc acc atg ttc tgc tcc att cat aaa aca gcc ctt cag act gca gaa	1824
Val Thr Met Phe Cys Ser Ile His Lys Thr Ala Leu Gln Thr Ala Glu	
595 600 605	
gtg agg agc cac atc ggg aag gag gtg gct gtt gca aac cgg ttc ttt	1872
Val Arg Ser His Ile Gly Lys Glu Val Ala Val Ala Asn Arg Phe Phe	
610 615 620	
ttt atc gtg ttc tct gat gcc atc tgc tgg atc cct gtg ttt gtc gtt	1920
Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val Val	
625 630 635 640	
aag atc ctg tct ctc ctt caa gtg gag ata cca ggc aca atc act tcc	1968
Lys Ile Leu Ser Leu Leu Gln Val Glu Ile Pro Gly Thr Ile Thr Ser	
645 650 655	
tgg atc gtg gtt ttt ttc ctt ccg gtg aac agc gcc tta aac ccc atc	2016
Trp Ile Val Val Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro Ile	
660 665 670	
ctc tac act ctg acg acc tcc ttt ttt aag gac aag ttg aaa cag ttg	2064
Leu Tyr Thr Leu Thr Thr Ser Phe Phe Lys Asp Lys Leu Lys Gln Leu	
675 680 685	
ctg cac aaa cat cgg agg aaa ccc atc ttc aaa gtt aag aag aaa agt	2112
Leu His Lys His Arg Arg Lys Pro Ile Phe Lys Val Lys Lys Lys Ser	
690 695 700	
tta tcc gct tcc att gtg tgg aca gac gag tct tca ctt aaa ctt gga	2160
Leu Ser Ala Ser Ile Val Trp Thr Asp Glu Ser Ser Leu Lys Leu Gly	
705 710 715 720	
gtg ttg agc aaa ata gcc ctt ggg gac agt ata atg aag ccg gtc tcc	2208
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Pro	

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 Asp Gly Val Asp Asp Cys Gly Asn Gly Ala Asp Glu Asp Asn Cys Gly
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 Asp Thr Ser Gly Trp Thr Thr Ile Phe Gly Thr Val His Gly Asn Val
 65 70 75 80
 Asn Lys Val Thr Leu Thr Gln Glu Cys Phe Leu Ser Gln Tyr Pro Gln
 85 90 95
 His Cys Tyr Cys Arg Glu Asn Glu Leu Glu Cys Val Lys Ala Asp Leu
 100 105 110
 Lys Ala Val Pro Lys Val Ser Ser Asn Val Thr Leu Leu Ser Leu Lys
 115 120 125
 Lys Asn Lys Ile His Arg Leu Pro Val Lys Val Phe Ser Arg Tyr Thr
 130 135 140
 Glu Leu Arg Lys Ile Tyr Leu Gln His Asn Cys Ile Thr His Ile Ser
 145 150 155 160
 Arg Arg Ala Phe Leu Gly Leu His Asn Leu Gln Ile Leu Tyr Leu Ser
 165 170 175
 His Asn Cys Ile Thr Ser Leu Arg Pro Gly Ile Phe Lys Asp Leu His
 180 185 190
 Gln Leu Ala Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser
 195 200 205
 Gln Lys Ser Phe Met Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val
 210 215 220
 Gly Asn Arg Leu Glu Ala Leu Pro Glu Thr Leu Cys Ala Gln Met Pro
 225 230 235 240
 Gln Leu Asn Trp Val Asp Leu Ala Asn Asn Gly Ile Lys Tyr Ile Thr
 245 250 255
 Asn Ser Thr Phe Leu Thr Cys Asp Ser Leu Thr Val Leu Phe Leu Pro
 260 265 270
 Arg Asn Gln Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys
 275 280 285
 Asn Leu Gly Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro
 290 295 300
 Val His Leu Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser
 305 310 315 320

Ser Asn Pro Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys
 325 330 335
 Gln Leu Gln Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Ser
 340 345 350
 Thr Gly Met Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Leu Lys
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 Thr Phe Arg Tyr Cys Ser Tyr Val Pro His Val Arg Ile Cys Met Pro
 370 375 380
 Ser Thr Asp Gly Ile Ser Ser Ser Glu Asp Leu Leu Ala Asn Gly Ile
 385 390 395 400
 Leu Arg Val Ser Val Trp Val Ile Ala Phe Ile Thr Cys Val Gly Asn
 405 410 415
 Phe Leu Val Ile Ala Val Arg Ser Leu Ile Lys Ala Glu Asn Thr Thr
 420 425 430
 His Ala Met Ser Ile Lys Ile Leu Cys Cys Ala Asp Cys Leu Met Gly
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 450 455 460
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 465 470 475 480
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 485 490 495
 Thr Phe Leu Thr Leu Glu Lys Phe Leu Val Ile Val Phe Pro Phe Ser
 500 505 510
 Asn Leu Arg Leu Gly Lys Arg Gln Thr Ala Val Ala Leu Ala Ser Ile
 515 520 525
 Trp Val Val Gly Phe Leu Ile Ala Ala Val Pro Phe Thr Arg Glu Asp
 530 535 540
 Tyr Phe Gly Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu His
 545 550 555 560
 Tyr Asp Gln Ala Glu Asp Phe Gly Ser Arg Gly Tyr Ser Leu Gly Ile
 565 570 575
 Phe Leu Gly Val Asn Leu Leu Ala Phe Leu Val Ile Val Ile Ser Tyr
 580 585 590
 Val Thr Met Phe Cys Ser Ile His Lys Thr Ala Leu Gln Thr Ala Glu
 595 600 605
 Val Arg Ser His Ile Gly Lys Glu Val Ala Val Ala Asn Arg Phe Phe
 610 615 620
 Phe Ile Val Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val Val
 625 630 635 640
 Lys Ile Leu Ser Leu Leu Gln Val Glu Ile Pro Gly Thr Ile Thr Ser

645								650				655			
Trp	Ile	Val	Val	Phe	Phe	Leu	Pro	Val	Asn	Ser	Ala	Leu	Asn	Pro	Ile
660								665				670			
Leu	Tyr	Thr	Leu	Thr	Thr	Ser	Phe	Phe	Lys	Asp	Lys	Leu	Lys	Gln	Leu
675								680				685			
Leu	His	Lys	His	Arg	Arg	Lys	Pro	Ile	Phe	Lys	Val	Lys	Lys	Lys	Ser
690								695				700			
Leu	Ser	Ala	Ser	Ile	Val	Trp	Thr	Asp	Glu	Ser	Ser	Leu	Lys	Leu	Gly
705								710				715			
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Pro

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Asp	Asp	Cys	Gly	Asn	Gly	Ala	Asp	Glu	Asp	Asn	Cys	Gly	Asp	Thr	Ser	
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Gly	Trp	Thr	Thr	Ile	Phe	Gly	Thr	Val	His	Gly	Asn	Val	Asn	Lys	Val	
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Thr	Leu	Thr	Gln	Glu	Cys	Phe	Leu	Ser	Gln	Tyr	Pro	Gln	His	Cys	Tyr	
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Cys	Arg	Glu	Asn	Glu	Leu	Glu	Cys	Val	Lys	Ala	Asp	Leu	Lys	Ala	Val	
				85					90					95		
Pro	Lys	Val	Ser	Ser	Asn	Val	Thr	Leu	Leu	Ser	Leu	Lys	Lys	Asn	Lys	
			100					105					110			
Ile	His	Arg	Leu	Pro	Val	Lys	Val	Phe	Ser	Arg	Tyr	Thr	Glu	Leu	Arg	
		115					120					125				
Lys	Ile	Tyr	Leu	Gln	His	Asn	Cys	Ile	Thr	His	Ile	Ser	Arg	Arg	Ala	
	130					135					140					
Phe	Leu	Gly	Leu	His	Asn	Leu	Gln	Ile	Leu	Tyr	Leu	Ser	His	Asn	Cys	
145					150					155					160	
Ile	Thr	Ser	Leu	Arg	Pro	Gly	Ile	Phe	Lys	Asp	Leu	His	Gln	Leu	Ala	
				165					170					175		
Trp	Leu	Ile	Leu	Asp	Asp	Asn	Pro	Ile	Thr	Arg	Ile	Ser	Gln	Lys	Ser	

180							185				190				
Phe	Met	Gly	Leu	Asn	Ser	Leu	Phe	Phe	Leu	Ser	Met	Val	Gly	Asn	Arg
	195						200					205			
Leu	Glu	Ala	Leu	Pro	Glu	Thr	Leu	Cys	Ala	Gln	Met	Pro	Gln	Leu	Asn
	210					215					220				
Trp	Val	Asp	Leu	Ala	Asn	Asn	Gly	Ile	Lys	Tyr	Ile	Thr	Asn	Ser	Thr
225					230					235					240
Phe	Leu	Thr	Cys	Asp	Ser	Leu	Thr	Val	Leu	Phe	Leu	Pro	Arg	Asn	Gln
				245					250					255	
Ile	Gly	Phe	Val	Pro	Glu	Lys	Thr	Phe	Ser	Ser	Leu	Lys	Asn	Leu	Gly
			260				265						270		
Glu	Leu	Asp	Leu	Ser	Ser	Asn	Met	Ile	Thr	Lys	Leu	Pro	Val	His	Leu
		275					280					285			
Phe	Ser	Asp	Leu	His	Leu	Leu	Gln	Lys	Leu	Asn	Leu	Ser	Ser	Asn	Pro
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Leu	Leu	Tyr	Val	His	Lys	Asn	Gln	Phe	Gly	Ser	Leu	Lys	Gln	Leu	Gln
305					310					315					320
Ser	Leu	Asp	Leu	Glu	Arg	Ile	Glu	Ile	Pro	Asn	Ile	Ser	Thr	Gly	Met
				325					330					335	
Phe	Gln	Pro	Met	Lys	Asn	Leu	Ser	His	Ile	Tyr	Leu	Lys	Thr	Phe	Arg
			340					345					350		
Tyr	Cys	Ser	Tyr	Val	Pro	His	Val	Arg	Ile	Cys	Met	Pro	Ser	Thr	Asp
		355					360					365			
Gly	Ile	Ser	Ser	Ser	Glu	Asp	Leu	Leu	Ala	Asn	Gly	Ile	Leu	Arg	Val
	370					375					380				
Ser	Val	Trp	Val	Ile	Ala	Phe	Ile	Thr	Cys	Val	Gly	Asn	Phe	Leu	Val
385					390					395					400
Ile	Ala	Val	Arg	Ser	Leu	Ile	Lys	Ala	Glu	Asn	Thr	Thr	His	Ala	Met
				405					410					415	
Ser	Ile	Lys	Ile	Leu	Cys	Cys	Ala	Asp	Cys	Leu	Met	Gly	Val	Tyr	Leu
			420				425						430		
Phe	Ser	Val	Gly	Val	Phe	Asp	Ile	Lys	Tyr	Arg	Gly	Gln	Tyr	Gln	Lys
		435					440					445			
Tyr	Ala	Leu	Leu	Trp	Met	Glu	Ser	Val	Pro	Cys	Arg	Leu	Leu	Gly	Phe
	450					455					460				
Leu	Ala	Thr	Leu	Ser	Thr	Glu	Val	Ser	Val	Leu	Leu	Leu	Thr	Phe	Leu
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Thr	Leu	Glu	Lys	Phe	Leu	Val	Ile	Val	Phe	Pro	Phe	Ser	Asn	Leu	Arg
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Leu	Gly	Lys	Arg	Gln	Thr	Ala	Val	Ala	Leu	Ala	Ser	Ile	Trp	Val	Val
			500					505					510		

Gly Phe Leu Ile Ala Ala Val Pro Phe Thr Arg Glu Asp Tyr Phe Gly
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 Asn Phe Tyr Gly Lys Asn Gly Val Cys Phe Pro Leu His Tyr Asp Gln
 530 535 540
 Ala Glu Asp Phe Gly Ser Arg Gly Tyr Ser Leu Gly Ile Phe Leu Gly
 545 550 555 560
 Val Asn Leu Leu Ala Phe Leu Val Ile Val Ile Ser Tyr Val Thr Met
 565 570 575
 Phe Cys Ser Ile His Lys Thr Ala Leu Gln Thr Ala Glu Val Arg Ser
 580 585 590
 His Ile Gly Lys Glu Val Ala Val Ala Asn Arg Phe Phe Phe Ile Val
 595 600 605
 Phe Ser Asp Ala Ile Cys Trp Ile Pro Val Phe Val Val Lys Ile Leu
 610 615 620
 Ser Leu Leu Gln Val Glu Ile Pro Gly Thr Ile Thr Ser Trp Ile Val
 625 630 635 640
 Val Phe Phe Leu Pro Val Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr
 645 650 655
 Leu Thr Thr Ser Phe Phe Lys Asp Lys Leu Lys Gln Leu Leu His Lys
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 His Arg Arg Lys Pro Ile Phe Lys Val Lys Lys Lys Ser Leu Ser Ala
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 ggg aat ctc acc aaa tgc ttg ccc cga gcc ttt cac tgc gat ggt gtg 96
 Gly Asn Leu Thr Lys Cys Leu Pro Arg Ala Phe His Cys Asp Gly Val
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 gat gat tgc ggg aat ggt gcc gac gag gac aac tgt ggt gac act agt 144
 Asp Asp Cys Gly Asn Gly Ala Asp Glu Asp Asn Cys Gly Asp Thr Ser

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Gly Trp Thr Thr Ile Phe Gly Thr Val His Gly Asn Val Asn Lys Val			
50	55	60	
aca ttg aca cag gag tgc ttt ctc agc cag tat cca cag cac tgt tac			240
Thr Leu Thr Gln Glu Cys Phe Leu Ser Gln Tyr Pro Gln His Cys Tyr			
65	70	75	80
tgc aga gaa aat gaa ctg gaa tgt gta aag gct gac tta aaa gct gtg			288
Cys Arg Glu Asn Glu Leu Glu Cys Val Lys Ala Asp Leu Lys Ala Val			
85	90	95	
cca aag gtt tcc agc aac gta aca tta cta tct ctt aag aaa aac aaa			336
Pro Lys Val Ser Ser Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys			
100	105	110	
atc cac aga ctt cca gtc aag gtc ttc agc aga tac aca gaa ctc aga			384
Ile His Arg Leu Pro Val Lys Val Phe Ser Arg Tyr Thr Glu Leu Arg			
115	120	125	
aag ata tac ctt cag cac aac tgc atc aca cac atc tcc agg aga gca			432
Lys Ile Tyr Leu Gln His Asn Cys Ile Thr His Ile Ser Arg Arg Ala			
130	135	140	
ttc ctt gga tta cat aat cta caa ata ctg tat ctc agc cat aac tgc			480
Phe Leu Gly Leu His Asn Leu Gln Ile Leu Tyr Leu Ser His Asn Cys			
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att acc tct ctc agg cct ggg ata ttc aaa gac ttg cat cag ctt gct			528
Ile Thr Ser Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Ala			
165	170	175	
tgg cta att tta gat gac aac ccg atc acc aga atc tca cag aag tcc			576
Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Lys Ser			
180	185	190	
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Phe Met Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Gly Asn Arg			
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ctc gag gcc ctt cct gaa aca ttg tgt gct cag atg cct caa ctc aac			672
Leu Glu Ala Leu Pro Glu Thr Leu Cys Ala Gln Met Pro Gln Leu Asn			
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Trp Val Asp Leu Ala Asn Asn Gly Ile Lys Tyr Ile Thr Asn Ser Thr			
225	230	235	240
ttc cta acg tgc gac tcg ctc acg gtt ctg ttt ctg cct aga aat caa			768
Phe Leu Thr Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln			
245	250	255	
att ggt ttt gtt cca gag aag aca ttt tct tca tta aaa aat tta gga			816
Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly			
260	265	270	
gaa ctg gac ctg tct agc aat atg ata aca aaa ctc cca gtc cac ctt			864
Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro Val His Leu			
275	280	285	

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 Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro
 290 295 300

 ctt ctg tat gtc cac aag aac cag ttt gga agt ctc aaa caa ctt cag 960
 Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys Gln Leu Gln
 305 310 315 320

 tct cta gac ctg gaa agg ata gag att cca aac ata agc aca gga atg 1008
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 325 330 335

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 340 345 350

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 Tyr Cys Ser Tyr Val Pro His Val Arg Ile Cys Met Pro Ser Thr Asp
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 Gly Trp Thr Thr Ile Phe Gly Thr Val His Gly Asn Val Asn Lys Val
 50 55 60

 Thr Leu Thr Gln Glu Cys Phe Leu Ser Gln Tyr Pro Gln His Cys Tyr
 65 70 75 80

 Cys Arg Glu Asn Glu Leu Glu Cys Val Lys Ala Asp Leu Lys Ala Val
 85 90 95

 Pro Lys Val Ser Ser Asn Val Thr Leu Leu Ser Leu Lys Lys Asn Lys
 100 105 110

 Ile His Arg Leu Pro Val Lys Val Phe Ser Arg Tyr Thr Glu Leu Arg
 115 120 125

 Lys Ile Tyr Leu Gln His Asn Cys Ile Thr His Ile Ser Arg Arg Ala
 130 135 140

 Phe Leu Gly Leu His Asn Leu Gln Ile Leu Tyr Leu Ser His Asn Cys
 145 150 155 160

Ile Thr Ser Leu Arg Pro Gly Ile Phe Lys Asp Leu His Gln Leu Ala
 165 170 175
 Trp Leu Ile Leu Asp Asp Asn Pro Ile Thr Arg Ile Ser Gln Lys Ser
 180 185 190
 Phe Met Gly Leu Asn Ser Leu Phe Phe Leu Ser Met Val Gly Asn Arg
 195 200 205
 Leu Glu Ala Leu Pro Glu Thr Leu Cys Ala Gln Met Pro Gln Leu Asn
 210 215 220
 Trp Val Asp Leu Ala Asn Asn Gly Ile Lys Tyr Ile Thr Asn Ser Thr
 225 230 235 240
 Phe Leu Thr Cys Asp Ser Leu Thr Val Leu Phe Leu Pro Arg Asn Gln
 245 250 255
 Ile Gly Phe Val Pro Glu Lys Thr Phe Ser Ser Leu Lys Asn Leu Gly
 260 265 270
 Glu Leu Asp Leu Ser Ser Asn Met Ile Thr Lys Leu Pro Val His Leu
 275 280 285
 Phe Ser Asp Leu His Leu Leu Gln Lys Leu Asn Leu Ser Ser Asn Pro
 290 295 300
 Leu Leu Tyr Val His Lys Asn Gln Phe Gly Ser Leu Lys Gln Leu Gln
 305 310 315 320
 Ser Leu Asp Leu Glu Arg Ile Glu Ile Pro Asn Ile Ser Thr Gly Met
 325 330 335
 Phe Gln Pro Met Lys Asn Leu Ser His Ile Tyr Leu Lys Thr Phe Arg
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 Gly Val Asp Asp Cys Gly Asn Gln Ala Asp Glu Asp Asn Cys Gly Asp
 50 55 60

Asn Asn Gly Trp Ser Met Gln Phe Asp Lys Tyr Phe Ala Ser Tyr Tyr
 65 70 75 80
 Lys Met Thr Ser Gln Tyr Pro Phe Glu Ala Glu Thr Pro Glu Cys Leu
 85 90 95
 Val Gly Ser Val Pro Val Gln Cys Leu Cys Gln Gly Leu Glu Leu Asp
 100 105 110
 Cys Asp Glu Thr Asn Leu Arg Ala Val Pro Ser Val Ser Ser Asn Val
 115 120 125
 Thr Ala Met Ser Leu Gln Trp Asn Leu Ile Arg Lys Leu Pro Pro Asp
 130 135 140
 Cys Phe Lys Asn Tyr His Asp Leu Gln Lys Leu Tyr Leu Gln Asn Asn
 145 150 155 160
 Lys Ile Thr Ser Ile Ser Ile Tyr Ala Phe Arg Gly Leu Asn Ser Leu
 165 170 175
 Thr Lys Leu Tyr Leu Ser His Asn Arg Ile Thr Phe Leu Lys Pro Gly
 180 185 190
 Val Phe Glu Asp Leu His Arg Leu Glu Trp Leu Ile Ile Glu Asp Asn
 195 200 205
 His Leu Ser Arg Ile Ser Pro Pro Thr Phe Tyr Gly Leu Asn Ser Leu
 210 215 220
 Ile Leu Leu Val Leu Met Asn Asn Val Leu Thr Arg Leu Pro Asp Lys
 225 230 235 240
 Pro Leu Cys Gln His Met Pro Arg Leu His Trp Leu Asp Leu Glu Gly
 245 250 255
 Asn His Ile His Asn Leu Arg Asn Leu Thr Phe Ile Ser Cys Ser Asn
 260 265 270
 Leu Thr Val Leu Val Met Arg Lys Asn Lys Ile Asn His Leu Asn Glu
 275 280 285
 Asn Thr Phe Ala Pro Leu Gln Lys Leu Asp Glu Leu Asp Leu Gly Ser
 290 295 300
 Asn Lys Ile Glu Asn Leu Pro Pro Leu Ile Phe Lys Asp Leu Lys Glu
 305 310 315 320
 Leu Ser Gln Leu Asn Leu Ser Tyr Asn Pro Ile Gln Lys Ile Gln Ala
 325 330 335
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 340 345 350
 Ile Glu Ile Ser Asn Ile Gln Gln Arg Met Phe Arg Pro Leu Met Asn
 355 360 365
 Leu Ser His Ile Tyr Phe Lys Lys Phe Gln Tyr Cys Gly Tyr Ala Pro
 370 375 380

His Val Arg Ser Cys Lys Pro Asn Thr Asp Gly Ile Ser Ser Leu Glu
 385 390 395 400
 Asn Leu Leu Ala Ser Ile Ile Gln Arg Val Phe Val Trp Val Val Ser
 405 410 415
 Ala Val Thr Cys Phe Gly Asn Ile Phe Val Ile Cys Met Arg Pro Tyr
 420 425 430
 Ile Arg Ser Glu Asn Lys Leu Tyr Ala Met Ser Ile Ile Ser Leu Cys
 435 440 445
 Cys Ala Asp Cys Leu Met Gly Ile Tyr Leu Phe Val Ile Gly Gly Phe
 450 455 460
 Asp Leu Lys Phe Arg Gly Glu Tyr Asn Lys His Ala Gln Leu Trp Met
 465 470 475 480
 Glu Ser Thr His Cys Gln Leu Val Gly Ser Leu Ala Ile Leu Ser Thr
 485 490 495
 Glu Val Ser Val Leu Leu Leu Thr Phe Leu Thr Leu Glu Lys Tyr Ile
 500 505 510
 Cys Ile Val Tyr Pro Phe Arg Cys Val Arg Pro Gly Lys Cys Arg Thr
 515 520 525
 Ile Thr Val Leu Ile Leu Ile Trp Ile Thr Gly Phe Ile Val Ala Phe
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 Ile Pro Leu Ser Asn Lys Glu Phe Phe Lys Asn Tyr Tyr Gly Thr Asn
 545 550 555 560
 Gly Val Cys Phe Pro Leu His Ser Glu Asp Thr Glu Ser Ile Gly Ala
 565 570 575
 Gln Ile Tyr Ser Val Ala Ile Phe Leu Gly Ile Asn Leu Ala Ala Phe
 580 585 590
 Ile Ile Ile Val Phe Ser Tyr Gly Ser Met Phe Tyr Ser Val His Gln
 595 600 605
 Ser Ala Ile Thr Ala Thr Glu Ile Arg Asn Gln Val Lys Lys Glu Met
 610 615 620
 Ile Leu Ala Lys Arg Phe Phe Phe Ile Val Phe Thr Asp Ala Leu Cys
 625 630 635 640
 Trp Ile Pro Ile Phe Val Val Lys Phe Leu Ser Leu Leu Gln Val Glu
 645 650 655
 Ile Pro Gly Thr Ile Thr Ser Trp Val Val Ile Phe Ile Leu Pro Ile
 660 665 670
 Asn Ser Ala Leu Asn Pro Ile Leu Tyr Thr Leu Thr Thr Arg Pro Phe
 675 680 685
 Lys Glu Met Ile His Arg Phe Trp Tyr Asn Tyr Arg Gln Arg Lys Ser
 690 695 700
 Met Asp Ser Lys Gly Gln Lys Thr Tyr Ala Pro Ser Phe Ile Trp Val

705		710		715		720
Glu Met Trp Pro Leu Gln Glu Met Pro Pro Glu Leu Met Lys Pro Asp						
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Leu Asn Ser Tyr Ser						
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 <213> Human immunodeficiency virus type 1

<400> 25
 Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
 1 5 10

<210> 26
 <211> 15
 <212> PRT
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: internalizing
 domain derived from HIV tat protein

<400> 26
 Gly Gly Gly Gly Tyr Gly Arg Lys Lys Arg Arg Gln Arg Arg Arg
 1 5 10 15

<210> 27
 <211> 34
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: PCR primer

<400> 27
 tgccaaaaag gatattttcc ctgtgggaat ctta 34

<210> 28
 <211> 47
 <212> DNA
 <213> Artificial Sequence

<220>
 <223> Description of Artificial Sequence: PCR primer

<400> 28
 ctaggaaact gggttcatta tactgtctcc aagtgttatt ttgttca 47

<210> 29

<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: RACE primer

<400> 29
ccatcctaatacgaactcactatagggc 27

<210> 30
<211> 32
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: RACE primer

<400> 30
attgtcatctagaattagccaggttagctgat 32

<210> 31
<211> 27
<212> DNA
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<220>
<223> Description of Artificial Sequence: RACE primer

<400> 31
aacaaggaattaatcccgtaaacaag 27

<210> 32
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<212> DNA
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<220>
<223> Description of Artificial Sequence: RACE primer

<400> 32
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<210> 33
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<400> 33
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<210> 34
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: RACE primer

<400> 34
atattccagg tctgagggtt gtgat 25

<210> 35
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<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 35
ctgctttgga aatctttttg tca 23

<210> 36
<211> 23
<212> DNA
<213> Artificial Sequence

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<400> 36
ttttccaggt cgaatgttac tga 23

<210> 37
<211> 20
<212> DNA
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<220>
<223> Description of Artificial Sequence: PCR primer

<400> 37
atgccttgct gtggatggag 20

<210> 38
<211> 19
<212> DNA
<213> Artificial Sequence

<220>
<223> Description of Artificial Sequence: PCR primer

<400> 38
acttcggtgg acagcatgg 19

<210> 39
<211> 20
<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:
oligonucleotide probe

<400> 39

cgtgcagtgc cgctcatgg

20

<210> 40

<211> 15

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primer

<400> 40

gtcgacggcg agccc

15

<210> 41

<211> 21

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: PCR primer

<400> 41

tctttgggac cttgtctgca a

21

<210> 42

<211> 22

<212> DNA

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence:
oligonucleotide probe

<400> 42

tgggccgcgt ctcttttgag ct

22